# EXHIBIT E
# (’565 Patent File Wrapper (excerpts))

E1

1848-32 US Track 1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicant: | American Regent, Inc. | Examiner: | To Be Assigned |
| Continuation of | | | |
| Serial No: | 17/365,695 | Art Unit: | To Be Assigned |
| Filed: | July 1, 2021 | Conf. No.: | To Be Assigned |
| For: | TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE | | |

March 21, 2023

**PRELIMINARY AMENDMENT**

Prior to examination on the merits, and calculation of claim fees, please enter the following Preliminary Amendment in conjunction with form PTO/AIA/424 for Track One Certification and Request for Prioritized Examination under C.F.R. 1.102(e) in the above-identified application.

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**CERTIFICATE OF EFS-WEB TRANSMISSION**

I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on March 21, 2023.

Date: March 21, 2023

/William D. Schmidt/
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**IN THE CLAIMS:**

1. (Currently Amended) An injectable composition comprising water, and ~~at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper,~~ about 4 µg to about 90 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, and no iron or iron in an amount up to about 10 µg ~~or about 1 µg to about 80 µg of manganese~~ per 1 mL of the injectable composition.

2. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition comprises ~~3,000 µg of zinc, 300 µg of copper,~~ about 60 µg of selenium~~, and 55 µg of manganese~~ per 1 mL of the injectable composition.

3. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition comprises ~~1000 µg of zinc, 60 µg of copper,~~ about 6 µg of selenium ~~and 3 µg of manganese~~ per 1 mL of injectable composition.

4. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~further comprising (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7, aluminum from~~ about 0.0001 to about 0.6 mcg of aluminum ~~/kg/day or a mixture thereof~~ per 1 mL~~; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof~~.

5. (Currently Amended) The injectable composition of claim 1, ~~further comprising (i)~~ wherein the injectable composition contains ~~iron from~~ about 0.0001 to about 10 µg/mL iron ~~, silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron from about 0.0001 to about 50 µg/mL or a mixture thereof; (ii) iron from about 0 to about 10 µg/mL, silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof; or (ii) wherein the zinc is elemental zinc, the~~

~~copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection~~.

6. (Original) The injectable composition of claim 1, wherein the composition has a pH of about 1.0 to about 5.

7. (Cancelled).

8. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 40 µg per 1 mL of selenium ~~at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.03 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.0055 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 99.66 wt. percent based on a total weight of the injectable composition~~.

9. (Currently Amended) The injectable composition of claim 2 [[8]], wherein the injectable composition has a pH of about 1.8 to about 2.4 ~~at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent based on a total weight of the injectable composition~~.

10. (Cancelled).

11. (Currently Amended) The injectable composition of claim [[1]] 3, wherein the injectable composition ~~comprises a preservative~~ has a pH of about 1.8 to about 2.4.

12. (Cancelled).

13. (Currently Amended) The injectable composition of claim [[5]] 1, wherein ~~the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, and the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and~~ the ~~elemental~~ selenium is elemental selenium from selenious acid.

14. (Currently Amended) The injectable composition of claim [[1]] 2, wherein the selenium is elemental selenium from selenious acid ~~injectable composition is in a multi-dose vial~~.

15. (Currently Amended) The injectable composition of claim [[14]] 3, wherein the selenium is elemental selenium from selenious acid ~~multi-dose vial contains 10 mL of the injectable composition~~.

16. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition ~~further comprises~~ contains about 0.0001 µg/mL to about 0.25 µg/mL of chromium.

17. (Original) The injectable composition of claim 1, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum.

18. (Currently Amended) The injectable composition of claim 1, wherein ~~the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and~~ the injectable composition contains ~~the selenium is selenious acid at a dose of~~ about [[20]] 6 to about 60 ~~µg/day~~ µg of selenium per 1 mL of the injectable composition.

19. (Currently Amended) The injectable composition of claim [[1]] 8, wherein ~~zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.15 to about 0.8 mg/day, and~~ the selenium is elemental selenium from selenious acid ~~at a dose of about 20 to about 40 µg/day~~.

20.- 55. (Cancelled)

56. (Currently Amended) A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, ~~and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper,~~ about 4 µg to about 90 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, and no iron or iron in an amount up to about 10 µg ~~or about 1 µg to about 80 µg of manganese~~ per 1 mL of the injectable composition.

57.- 62. (Cancelled)

63. (Currently Amended) The injectable composition of ~~claims 1-38~~ claim 2, wherein the injectable composition is ~~administered to a human~~ suitable for administration to an adult or pediatric patient.

64. (Currently Amended) The method of claim ~~39-62~~ 56, wherein the injectable composition is suitable for administration ~~administered~~ to a human patient that is an adult, pediatric or neonatal patient.

65. (Currently Amended) [[An]] The injectable ~~trace element~~ composition of claim 3, wherein the injectable composition is suitable for administration to a pediatric or neonatal patient ~~comprising water, about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition~~.

66. (Currently Amended) The injectable composition of claim 1, further comprising nitric acid ~~wherein zinc comprises from about 800 µg to about 4000 µg per 1mL of the injectable composition~~.

67. (Currently Amended) The injectable composition of claim [[1]] 2, further comprising nitric acid ~~wherein copper comprises from about 40 µg to about 400 µg per 1mL of the injectable composition~~.

68. (Currently Amended) The injectable composition of claim [[1]] 3, further comprising nitric acid ~~wherein selenium comprises from about 4 µg to about 90 µg per 1mL of the injectable composition~~.

69. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition is in a volume that fills a 1 mL, 2 mL, 3 mL, 5 mL or 10 mL vial ~~manganese comprises from about 1 µg to about 80 µg per 1mL of the injectable composition~~.

70. (Currently Amended) The injectable composition of claim [[1]] 8, further comprising nitric acid ~~wherein the zinc, copper, selenium, manganese are in elemental or salt form~~.

71.-73. (Cancelled)

74. (Original) The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium.

75. (Currently Amended) The injectable composition of claim 1, wherein [[the]] permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/

day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

76. (New) An injectable composition consisting of water, nitric acid, selenious acid 98 µg as an active ingredient, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, and no iron or iron in an amount up to about 10 µg per 1 mL of the injectable composition.

77. (New) An injectable composition consisting of water, nitric acid, selenious acid 9.8 µg as an active ingredient, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, and no iron or iron in an amount up to about 10 µg per 1 mL of the injectable composition.

## REMARKS

Prior to examination on the merits, and calculation of claim fees, please enter this Preliminary Amendment. Claims 1 and 56 have been amended to include that the injectable composition comprises selenium and that there is no chromium or chromium not to exceed 1µg, there is no aluminum or aluminum in an amount not to exceed 6 µg, and there is no iron or iron in an amount up to about 10 µg per 1 mL of the injectable composition. These are impurity amounts of chromium, aluminum, and iron. Support for the amendment can be found throughout the specification at least at paragraphs [0073], [0087], [0093] and Table 2 of the specification and claim 5.

Claims 2, 3, and 18 have been amended to include that the injectable composition contains a specific amount of selenium already recited in the claims. Claim 4 has been amended to include that the injectable composition contains a specific amount of aluminum impurity already recited in the claim. Claim 5 has been amended to include that the injectable composition has a specific amount of iron impurity already recited in the claim. Claim 8 has been amended to include that the injectable composition comprises about 40 µg of selenium per 1 mL of the injectable composition. Support for the amendment to claim 8 can be found throughout the specification at least at paragraphs [0060], [0061] and [0065] of the specification.

Claims 9 and 11 have been amended to include that the pH of the injectable composition is about 1.8 to about 2.4. Support for the amendment can be found throughout the specification at least at paragraphs [0088], [0112], [0132], [0163] and Table 5 of the specification.

Claims 13-15 and 19 have been amended to include that the selenium of the injectable composition is elemental selenium from selenious acid. Support for the amendment can be found throughout the specification at least at paragraphs [0060], [0061], [0065]-[0067], [0161]-[0167], [0280], [0290], Tables 1, 5, 6, and 26 of the specification and claims 13, 18, 19, 36-38, 49 and 54-55.

Claims 63-65 have been amended to include that the injectable composition is suitable for administration to adult, pediatric, or neonatal patients. Support for the amendment can be found throughout the specification at least at paragraphs [0278], [0289], [0296], Example 11 and Table 35 of the specification.

Claims 66-68 and 70 have been amended to include that the injectable composition contains nitric acid. Support for the amendment can be found throughout the specification at least at paragraphs [0112] and [0164] of the specification.

Claim 69 has been amended to include that the injectable composition is in a volume that fills a 1 mL, 2 mL, 3 mL, 5 mL or 10 mL vial. Support for the amendment can be found throughout the specification at least at paragraphs [0093], [0099], [0123], [0129], [0146], Table 5 and claim 15 of the specification.

New claims 76 and 77 have been added to include a specific injectable composition consisting essentially of 98 µg of selenious acid or 9.8 µg of selenious acid as the active ingredient, respectively and that there is no chromium or chromium not to exceed 1µg, there is no aluminum or aluminum in an amount not to exceed 6 µg, and there is no iron or iron in an amount up to about 10 µg per 1 mL of the injectable composition. Support for the amendment can be found throughout the specification at least at paragraphs [0013], [0022], [0066], [0073], [0087], [0091], [093], [0110], [0112], [0186], [0197], [0284], [0290] Tables 1, 2 and 6 of the specification and claims 5, 33, 34 and 38.

Claims 7, 10, 12, 20-55, 57-62, and 71-73 have been cancelled, without disclaimer. Applicant reserves the right to pursue these claims in one or more continuing applications. This Preliminary Amendment has 29 claims in total, with 4 of those claims as independent claims. This Preliminary Amendment does not add new matter.

**No Disclaimers or Disavowals**

Although the present communication may include alterations to the claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited reference. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history may not

reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

**Conclusion**

No fee is believed to be due with respect to the filing of this Preliminary Amendment, except the fee for a total of 9 additional claims over 20 claims, 1 extra independent claim over 3 and the Track I processing fee. If the Examiner determines that any further action is necessary to place this application into better form, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided.

Respectfully submitted,

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**PATENT**
**Docket No.: 1848-32 US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION FOR UNITED STATES LETTERS PATENT

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**TITLE: TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE**

ASSIGNEE: American Regent, Inc.

Docket No.: 1848-32 US

# TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE

**[0001]** This application claims priority to U.S. Provisional Application Serial No. 63/047,708, filed on July 2, 2020, the entire disclosure of which is hereby incorporated by reference in its entirety into the present disclosure.

## BACKGROUND

**[0002]** Parenteral nutrition (PN) provides nutrients and fluids to a patient and is typically administered intravenously. It differs from normal oral food ingestion in that the nutrients and fluids are administered by an intravenous infusion. In this way, the entire digestive tract is bypassed. Parenteral nutrition is indicated when ingestion of nourishment administered orally via the digestive tract is not possible, not desired, or too dangerous. Thus, parenteral nutrition is used when there are considerable impediments in digestion and resorption, as well as in the framework of intensive care medicine. Complete parenteral nutrition can supply the same nutrients as normal enteral nourishment which includes carbohydrates, fats, proteins, vitamins, electrolytes, water and also trace elements (e.g., trace metals).

**[0003]** Trace elements together with vitamins are required for specific metabolic functions. Trace elements are present at very low concentrations in the human body and help maintain physical and mental health. As structural and/or functional constituents of numerous metalloproteinases (e.g., copper, zinc), enzymes (e.g., selenium), hormones (e.g., iodine) or vitamins (e.g., cobalt), trace elements are involved in many metabolic processes. A deficiency of trace elements impairs the optimal development of important physiological processes in the body.

**[0004]** Often times, one or more trace elements are added to the parenteral nutrition using specific pharmaceutical manufacturing regulations under strict aseptic conditions. Trace element addition to the parenteral nutrition is an important component in the framework of parenteral nutrition therapy. Trace element addition can also remedy an already existing trace element deficiency to help the patient have an enhanced quality of life. Although trace element addition facilitates many enzymatic processes, long term use may cause accumulation of large quantities resulting in toxicity.

**[0005]** In recent years, recommended daily doses of trace elements (e.g., copper, manganese, and chromium) have been reduced and some instances daily doses of chromium are not typically needed. Sometimes, the daily dosage of trace elements needs to be adjusted for contaminants that may already be present in the parenteral nutrition.

**[0006]** Because multiple trace elements (e.g., zinc, copper, selenium, manganese, and chromium) are currently available in all-in-one formulations at higher daily doses, one or more trace elements are not easily customizable to the patient's specific trace element requirement when it is added to the parenteral nutrition.

**[0007]** Typically, parenteral nutrition once admixed remains stable for a relatively short period of time without the addition of trace elements to the parenteral nutrition. For example, once admixed, KABIVEN® parenteral nutrition remains stable for 48 hours at room temperature or 25°C. This stability is without the addition of trace elements to the parenteral nutrition. If not used immediately, the admixed KABIVEN® parenteral nutrition can be stored for up to 7 days under refrigeration at 2°C to 8°C without the addition of trace elements to the parenteral nutrition. After removal from refrigeration, the admixed KABIVEN® parenteral nutrition should be used within 48 hours. If not, it should be discarded. This type of stability is also for other different brands of parenteral nutrition.

**[0008]** Parenteral nutrition is admixed based on the specific metabolic needs of the patient. Admixing parenteral nutrition can be time consuming, expensive, and tedious to prepare under aseptic conditions. Often when trace elements are added to parenteral nutrition and the parenteral nutrition is stored for more than 24 to 48 hours at room temperature, stability problems such as, for example, particulate formation and precipitation may occur. This requires the healthcare provider (e.g., pharmacist, nurse, healthcare facility, caregiver, etc.) to dispose of any unused parenteral nutrition after the 24 to 48-hour time period, which increases cost to the patient and the healthcare provider.

**[0009]** Further, if the patient's parenteral nutrition is put on hold for a short period of time (e.g., 48 hours); the admixed parenteral nutrition containing the added trace elements will also need to be discarded. This can lead to drug supply shortages as now the parenteral nutrition and trace elements have to be discarded and a new prescription of parenteral nutrition containing the trace elements has to be admixed again. Because of the short stability period, parenteral nutrition with added trace elements is prepared close to the time period that it will be administered to the patient on a daily basis, which may require frequent trips to the healthcare facility. This also prevents the parenteral nutrition with added trace elements to be made in many daily doses or in batches.

**[0010]** Thus, there is a need for injectable parenteral nutrition containing one or more trace elements that is stable for a longer period of time, thereby reducing the time and costs associated with frequent admixing. The quality of life of the patient and the caregiver is also improved by avoiding frequent trips to healthcare facilities for the admixing of injectable parenteral nutrition. Further, there is also a

need for parenteral nutrition with one or more added trace elements that can be made in many daily doses or in batches because it is stable for a longer period of time. There is also a need for trace element compositions and methods that have lower daily doses of one or more trace elements compared to those in currently available trace element products.

## SUMMARY

**[0011]** An injectable parenteral nutrition containing a trace element is provided that is stable for a longer period of time compared to existing parenteral nutrition products that have trace elements added thereto, thereby reducing the time and costs associated with frequent admixing. The quality of life of the patient and the caregiver is also improved by avoiding frequent trips to healthcare facilities for the admixing of injectable parenteral nutrition. An injectable parenteral nutrition containing a trace element is also provided that can be made in daily doses or in batches because it is stable for a longer period of time. There is also provided a trace element composition and method that have lower daily doses of one or more trace elements as compared to currently available trace element products (e.g., Mutitrace-5® concentrate, Addamel™) that can be dosed for adult, pediatric or neonatal patients.

**[0012]** In one embodiment there is an injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0013]** In another embodiment, there is an injectable composition comprising water, and at least one trace element consisting of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0014]** In yet another embodiment, there is a method of making an injectable composition, the method comprising mixing at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese with water to form 1 mL of the injectable composition.

**[0015]** In still yet another embodiment, there is a method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, and at least one of about 800 µg to about 4,000

µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0016]** In one exemplary embodiment, there is an injectable trace element composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0017]** In various embodiments, the injectable compositions described in this application comprise, consist essentially of or consist of water, at least one of zinc in an amount from about 600 ug, 700 ug, or 800 µg to about 4,000 µg, copper in an amount from about 40 µg to about 400 µg, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0018]** Stable trace element injectable compositions or injectable compositions that can be added to a parenteral nutrition are provided. In various aspects, a stable injectable composition comprises water, from about 800 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable. In some aspects, the stable trace element injectable composition consists essentially of or consists of water, from about 900 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable.

**[0019]** In some embodiments, methods of making and using the stable injectable compositions of this application are provided. In one aspect, the method of making a trace element injectable composition includes mixing from about 800 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese with water to form 1 mL of the injectable composition.

**[0020]** In some embodiments, there is a method of maintaining plasma trace elements in a patient in need thereof, the method including administering at least an injectable composition to the patient, the injectable composition comprising water, from about 800 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0021]** In various aspects, stable parenteral nutrition is provided comprising at least one of an amino acid, a dextrose, a lipid, water, an electrolyte, or a mixture thereof and at least one trace element which is stable for about at least 3 days to about 14 days. In various embodiments, the at least one trace element of the stable parenteral nutrition includes zinc, copper, selenium, and manganese or a mixture thereof.

**[0022]** In many embodiments, parenteral nutrition comprises, consists essentially of, or consists of an amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof and at least one trace element composition per from about 250 mL to about 4000 mL of parenteral nutrition. The stable trace element injectable composition that can be added to a parenteral nutrition comprises, consists essentially of or consists of water, from about 800 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable. In some embodiments, the trace element injectable composition that can be added to parenteral nutrition contains water for injection and trace elements comprising, consisting essentially of or consisting of from about 2000 µg to about 4,000 µg of zinc, from about 200 µg to about 400 µg of copper, from about 30 µg to about 90 µg of selenium and from about 20 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0023]** In some embodiments, the trace element injectable composition comprises, consists essentially of, or consists of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition. These trace element compositions are useful additives to parenteral nutrition for adult or pediatric patients.

**[0024]** In yet other embodiments, the stable trace element composition that can be added to parenteral nutrition comprises, consists essentially of or consists of 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of the injectable composition. These trace element compositions are useful additives to parenteral nutrition for neonate patients.

**[0025]** In various embodiments, the injectable compositions including trace elements can be added to parenteral nutrition available in the marketplace, for example KABIVEN® and CLINIMIX®. As a result, this application provides parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof and at least one of zinc, copper, selenium, and manganese, which is stable for about at least 3 days to about 14 days.

**[0026]** In some embodiments, there is a method of making a parenteral nutrition containing trace elements, the method comprising adding trace elements to the parenteral nutrition, the trace elements comprising about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 250 mL to about 4000 mL of the parenteral nutrition, the parenteral nutrition comprising at least one of amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof.

**[0027]** In some aspects, there is a method of providing a source of calories, protein, electrolytes, water or essential fatty acids for adult, pediatric or neonate patients requiring parenteral nutrition, the method comprising administering to a patient in need thereof an injectable parenteral nutrition formulation comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof, the parenteral nutrition comprising about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 250 mL to 4000 mL of the parenteral nutrition.

**[0028]** In some embodiments, there is a method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering a parenteral nutrition to the patient, the parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof and at least one of zinc, copper, selenium, and manganese, which is stable for about at least 3 days to about 14 days to prevent depletion of endogenous stores of the at least one of zinc, copper, selenium, and manganese and subsequent depletion symptoms.

**[0029]** A method of maintaining, supplementing or increasing one or more trace elements to a patient in need thereof, the method comprising administering to the patient about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per about 250 mL to 4000 mL of aqueous fluid, the aqueous fluid comprising an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof.

**[0030]** Additional features and advantages of various embodiments will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of various embodiments. The objectives and other advantages of various embodiments will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

DETAILED DESCRIPTION

Definitions

**[0031]** For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities of ingredients, percentages or proportions of materials, reaction conditions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

**[0032]** Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the disclosure are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a range of "1 to 10" includes any and all subranges between (and including) the minimum value of 1 and the maximum value of 10, that is, any and all subranges having a minimum value of equal to or greater than 1 and a maximum value of equal to or less than 10, e.g., 5.5 to 10.

**[0033]** Scientific and technical terms used herein have meanings commonly used in the art unless otherwise specified. The definitions provided herein are to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

**[0034]** It is noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the," include plural referents unless expressly and unequivocally limited to one referent. Thus, for example, reference to "a trace element" includes one, two, three or more trace elements.

**[0035]** As used in this specification and the appended claims, the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

**[0036]** Patents, patent applications, published applications and publications, websites and other

published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

**[0037]** The term "composition(s)" refers to an aggregate material formed from two or more substances, ingredients, or constituents; the way in which a whole or mixture is made up. When referring to pharmaceutical drug products, a composition is often called "formulation(s)".

**[0038]** The term "impurity" refers to a constituent, component or ingredient which impairs the purity of a pharmaceutical active ingredient or pharmaceutical composition.

**[0039]** The term "injectable" or "injectable composition," as used herein, means a composition that can be injected into a larger volume container and infused intravenously via peripheral veins found in upper extremities (hands and arms) or central veins, which is a large vein in the central circulation system. Catheters are used to reach either a peripheral or central vein. For example, central venous catheters can be inserted percutaneously or surgically through the jugular, subclavian, or femoral veins, or via the chest or upper arm peripheral veins.

**[0040]** The trace elements composition can be administered parenterally including intravenously or the like into the patient (e.g., mammal). The term "mammal" refers to organisms from the taxonomy class "mammalian," including but not limited to humans, other primates such as monkeys, chimpanzees, apes, orangutans and monkeys, rats, mice, rabbits, cats, dogs, pigs, cows, horses, etc.

**[0041]** The term "reference listed drug" refers to an approved drug product to which generic versions are compared to show that they are bioequivalent.

**[0042]** The term "stability" refers to capability of a pharmaceutical active ingredient or pharmaceutical composition to remain within a specific criteria or specification(s).

**[0043]** The term "stable", as used herein, means remaining in a state or condition that is suitable for administration to a patient and without undergoing a substantial change in the potency of the active agent in the formulation over the specified time period. In some embodiments, the injectable parenteral nutrition composition containing trace elements of the current application is considered stable if the parenteral nutrition composition containing trace elements can maintain its strength at the level specified on the label for the maximum anticipated shelf-life (e.g., the time period from the date of

manufacture until administration to the animal, for example, a human patient) under environmental conditions likely to be encountered in actual use. Typically, stability can be determined following the FDA guidelines, for example, Guidance for Industry: Drug Stability Guidelines (p. 1-48), December 9, 2008.

**[0044]** A substantial change in potency is one which decreases the drug concentration by more than 15%, from the target concentration for the specified period of time. Unless indicated otherwise, a stable composition is one which retains at least 85% of the original amount of the injectable composition in that state (e.g., not precipitated, degraded, or adsorbed to the container) for a period of at least 72 hours.

**[0045]** The carriers and excipients and other components of the pharmaceutical compositions must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Thus, the term "pharmaceutically acceptable salt" references salt forms of the active compounds which are prepared with counter ions which are non-toxic under the conditions of use and are compatible with a stable formulation. For compounds which contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent.

**[0046]** The term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that has an acceptable side-effect profile and serves to provide a medium for the storage or administration of the active component(s) under the conditions of administration for which the composition is formulated or used. The carrier or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. For the injectable compositions of this disclosure, water is a pharmaceutically acceptable carrier. There are a wide variety of suitable formulations of pharmaceutical compositions of the present disclosure (see, e.g., Remington's Pharmaceutical Sciences, 20th ed., 2018, supra).

**[0047]** The term "tonicity adjusting agents" refers to agents used to modify the osmolality of a formulation to bring it closer to the osmotic pressure of body fluids such as blood or plasma. Provided that the compositions are physiologically compatible, the compositions do not require any particular

osmolality. Thus, the compositions can be hypotonic, isotonic, or hypertonic. Typically, the pharmaceutical compositions have an osmolality between about 250 to 350 mOsm/kg. The tonicity of the pharmaceutical compositions can be adjusted by adjusting the concentration of any one or more of a tonicity agent, a co-solvent, complexing agent, buffering agent, or excipient. Suitable tonicity adjusting agents include, but are not limited to, anhydrous and hydrous forms of dextrose, for example, dextrose 5%, dextrose 10%, dextrose 20 %, dextrose 25%, or dextrose 50% in water or a combination thereof.

**[0048]** The pH of the injectable composition can be adjusted to the recited pH range or target pH by the addition of an acid or acidic salt or base or basic salt, as appropriate. For instance, the pH may be adjusted with a base such as an alkali metal hydroxide such as NaOH, KOH, or LiOH, or an alkaline earth metal hydroxide, such as Mg(OH)2 or Ca(OH)2, or a carbonate. Acids useful for adjusting the pH include, without limitation, hydrochloric acid, or sulfuric acid, for example.

**[0049]** The term "pharmaceutical composition" is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients described herein.

**[0050]** The term "single-use container" refers to a sealed pharmaceutically prepared container holding a drug product in a sterile environment that is intended to be used in a single operation of transferring the entire contents or substantially entire contents. It should be recognized that the single-use container is generally preservative-free and that if multiple transfers are attempted, they should be completed in a short duration, i.e., less than about 8-10 hours from the first breach of the sterile environment. In some aspects the single-use container may be used to administer all of its contents to one subject in need thereof. In some aspects the single-use container may be used to administer its contents to more than one subject in need thereof.

**[0051]** As used herein, the term "mixing" refers to admixing, contacting, blending, stirring, or allowing to admix, mix, blend, stir and the like.

**[0052]** The term "dissolved oxygen" refers to oxygen that is found in the aqueous carrier of the compositions. Distinguished from dissolved oxygen is the headspace oxygen. As used herein, the term "headspace oxygen" refers to the oxygen that is found in the headspace volume of the sealed container comprising the composition.

**[0053]** It will be apparent to those skilled in the art that various modifications and variations can be made to various embodiments described herein without departing from the spirit or scope of the teachings herein. Thus, it is intended that various embodiments cover other modifications and variations of various embodiments within the scope of the present teachings.

**[0054]** The headings below are not meant to limit the disclosure in any way; embodiments under anyone heading may be used in conjunction with embodiments under any other heading.

Trace Elements Injectable Compositions

**[0055]** This application relates to the development of injectable compositions comprising at least one of zinc, copper, manganese, and selenium. The injectable compositions of this application include lower daily amounts of at least one of zinc, copper, manganese, chromium, or selenium per 1mL of the composition than currently available products.

**[0056]** Trace elements, such as zinc, copper, manganese, and selenium are important to metabolic functions and for restoring and maintaining normal growth and development in mammals. Zinc is a trace element. Zinc is a constituent of numerous enzymes including carbonic anhydrase, alcohol and lactate dehydrogenases and various peptidases. Zinc has been identified as a cofactor for over 70 different enzymes, including alkaline phosphatase, lactic dehydrogenase and both RNA and DNA polymerase. Zinc facilitates wound healing, helps maintain normal growth rates, normal skin hydration and the senses of taste and smell. Zinc is considered an essential nutrient participating in multiple metalloenzymes involved in most central metabolic pathways, including metabolism of protein, fat, and carbohydrates; DNA binding; gene regulation; transcription of DNA to RNA; synthesis of heme, long-chain fatty acids, and prostaglandins; cholesterol transport; stabilization of cell membrane lipids; sexual maturation and reproduction; and immune function.

**[0057]** Copper is a trace element. Copper is essential as a cofactor for serum ceruloplasmin, an oxidase necessary for proper formation of the iron carrier protein, transferrin. Copper also helps maintain normal rates of red and white blood cell formation. The metabolic functions of copper relate to its presence in tyrosinase, urate oxidase, dopamine-β-hydroxylase, amine oxidases, cytochrome oxidase and cytoplasmic superoxide dismutase, in the latter, in combination with zinc. Copper is incorporated into metalloenzymes that are involved with connective tissue formation; metabolism of iron (ceruloplasmin), cholesterol, and glucose; myelin synthesis; conversion of dopamine to norepinephrine in the brain, serotonin synthesis, melanin pigment formation; and antioxidant

participating in the immune system.

**[0058]** Manganese is another trace element. Manganese is believed to have an activating function for many enzymes such as phosphoglucomutase, choline esterase, the oxidative β-keto-decarboxylases, certain peptidases, and muscle ATPase. Manganese is an activator for enzymes such as polysaccharide polymerase, liver arginase, cholinesterase, and pyruvate carboxylase. Manganese is incorporated into metalloenzymes involved with energy release, fatty acid and cholesterol synthesis, and release of lipids from the liver.

**[0059]** Selenium is also a trace element. Selenium is part of glutathione peroxidase which protects cell components from oxidative damage due to peroxides produced in cellular metabolism. Selenium is incorporated at the active site of glutathione peroxidase, an enzyme that catalyzes the breakdown of hydroperoxides and has metabolic interrelationships with vitamin E, an antioxidant (Vanek et al., A.S.P.E.N. Position Paper, Nutrition in Clinical Practice, Vol. 27, No. 4, pp. 440-491, August 2012).

**[0060]** In various embodiments, the injectable compositions described in this application comprise, consist essentially of or consist of water, at least one of zinc in an amount from about 900 µg to about 4,000 µg, copper in an amount from about 40 µg to about 400 µg, selenium in an amount from about 4 µg to about 90 µg, or manganese in an amount form about 1 µg to about 80 µg per 1 mL of the injectable composition. Therefore, the injectable composition, in some embodiments, can have as the trace element zinc only, copper only, selenium only, manganese only or they can be in the composition in any combination.

**[0061]** In some embodiments, the injectable compositions described in this application comprise water, and at least one of zinc in an amount from about 2000 µg to about 4,000 µg, copper in an amount from about 200 µg to about 400 µg, about 30 µg to about 90 µg of selenium, and about 20 µg to about 80 µg of manganese per 1 mL of the injectable composition. In some other embodiments, zinc is in an amount from about 900 µg, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900 to about 4000 µg. In various embodiments, copper is in an amount from about 40 µg, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390 to about 400 µg. In other embodiments, selenium is in an amount from about 4 µg, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80 to about 90 µg. In yet other embodiments, manganese is in an amount from about 1 µg, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70 to about 80 µg. In various embodiments, the injectable compositions described in this

application comprise, consist essentially of or consist of water, zinc in an amount from about 2000 µg to about 4,000 µg, copper in an amount from about 200 µg to about 400 µg, about 30 µg to about 90 µg of selenium, and about 20 µg to about 80 µg of manganese per 1 mL of the injectable composition.

**[0062]** In some embodiments, the injectable composition comprises water, and at least one of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition. In other embodiments, the injectable composition consists essentially of or consists of water, 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition. These embodiments are useful as additives to parenteral nutrition applicable to adults or pediatric patients.

**[0063]** In other embodiments, the injectable composition comprises water 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition. In yet other embodiments, the trace element injectable composition consist essentially of or consists of water, 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition. These embodiments are useful as additives to parenteral nutrition applicable to neonate patients.

**[0064]** In various aspects the injectable composition includes only one of the trace elements, for example only zinc or copper, or manganese or selenium. The at least one of the zinc can include from about 0.23 wt. percent to about 1.33 wt. percent. The at least one of copper can be in an amount from about 0.03 wt. percent to about 0.13 wt. percent. The at least one of manganese comprises from about 0.0055 wt. percent to about 0.013 wt. percent. The at least one of selenium comprises about 0.002 wt. percent to about 0.02 wt. percent and the water comprises from about 96 wt. percent to about 99.66 wt. percent of the injectable composition based on a total weight of the injectable composition. In yet other embodiments, at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent of the injectable composition based on a total weight of the injectable composition.

**[0065]** In many aspects, the zinc in the injectable composition is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection. In other instances, the elemental zinc is obtained from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is generated from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate

and the elemental selenium is obtained from selenious acid. The injectable composition described in this application contains, in some aspects, zinc obtained from zinc sulfate heptahydrate, wherein the zinc and is at a dose of from about 2.5 to about 7 mg/day. The copper of the injectable composition can be obtained from cupric sulfate pentahydrate and is at a dose of from about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate and is at a dose of about 0.015 to about 0.08 mg/day, and the selenium is obtained from selenious acid and is at a dose of from about 20 to about 60 µg/day. In other aspects, the injectable composition contains zinc from zinc sulfate heptahydrate, wherein the zinc is at a dose of from about 2.5 to about 7 mg/day, the copper is obtained from cupric sulfate pentahydrate and is at a dose of from about 0.5 to about 1.5 mg/day, the manganese is obtained from manganese sulfate monohydrate and is at a dose of from about 0.15 to about 0.8 mg/day, and the selenium is obtained from selenious acid and is at a dose of about 20 to about 40 µg/day.

**[0066]** In various aspects, the trace elements of the compositions of this application comprise, consist essentially of or consist of zinc sulfate or zinc sulfate heptahydrate in an amount of from about 13.1 mg (13000 µg) to about 13.3 mg, cupric sulfate or cupric sulfate pentahydrate in an amount of about 1.1 mg to about 1.2 mg, manganese sulfate or manganese sulfate monohydrate in an amount of about 0.16 mg to about 0.18 mg and selenious acid in an amount of about 95 µg to about 99 µg per 1 mL of the injectable composition. In other aspects, in the injectable compositions, the trace elements comprise, consist essentially of or consist of zinc sulfate or zinc sulfate heptahydrate in an amount of from about 13.1 mg (13000 µg) to about 13.3 mg, cupric sulfate or cupric sulfate pentahydrate in an amount of from about 1.1 mg to about 1.2 mg, manganese sulfate or manganese sulfate monohydrate in an amount of from about 0.016 mg to about 0.018 mg and selenious acid in an amount of from about 95 µg to about 99 µg per 1 mL of the injectable composition. In yet other aspects, the zinc sulfate or zinc sulfate heptahydrate is in an amount of about 13.2 mg, the cupric sulfate or the cupric sulfate pentahydrate is in an amount of about 1.179 mg, the manganese sulfate or manganese sulfate monohydrate is in an amount of about 0.169 mg and the selenious acid is in an amount of about 98 µg per 1 mL of the injectable composition.

**[0067]** Zinc Sulfate heptahydrate is available from Avantor Performance Materials, LLC in Phillipsburg, NJ. Cupric sulfate pentahydrate USP can be obtained from Merck KGaA in Germany. Manganese sulfate monohydrate is available from Merck KGa in Germany. Selenious acid is available from Sigma Aldrich.

**[0068]** The trace elements composition can be added to one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof and administered to the patient parenterally (e.g., intravenously). Typically, the trace elements composition can be administered by intravenous infusion. For example, the trace elements composition can be added to parenteral nutrition and administered intravenously where about 100 mL to 4000mL can be administered via IV infusion over, for example, about 4 hours to 24 hours, or about 8 hours to 48 hours to the patient.

**[0069]** One embodiment of the trace elements injectable composition of this application useful for adult or pediatric patients is summarized in Table 1.

**[0070]** Table 1 - Injectable Composition

| **Ingredient (Name and Quality Standard)** | **Function** | **Quantity per mL** | **% w/v** | **Elemental Equivalent** |
|---|---|---|---|---|
| Zinc Sulfate • $7H_2O$, USP | Active | 13.20 mg | 1.320% | 3 mg Zn/mL |
| Cupric Sulfate • $5H_2O$, USP | Active | 1.18 mg | 0.118% | 0.3 mg Cu/mL |
| Manganese Sulfate •$H_2O$, USP | Active | 169 mcg | 0.017% | 55 µg Mn/mL |
| Selenious Acid, USP | Active | 98 mcg | 0.010% | 60 µg Se/mL |
| Sulfuric Acid, NF | pH adjustment | N/A | N/A | N/A |
| Water for Injection, USP | Solvent | q.s. to 1 mL | 98.535% | N/A |

N/A refers to not applicable; USP refers to United States Pharmacopeia; NF refers to National Formulary.

Elemental Impurities of Trace Elements Injectable Composition

**[0071]** The trace elements injectable composition, USP is a compendial drug product. Consequently, the characteristics of the injectable composition are based on the drug product release specifications established by the compendial monograph for the product, FDA guidance, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommendations. The drug product release specifications, which include all critical drug product attributes, are illustrated in Table 2.

**[0072]** Table 2 - Specifications and Properties of Trace Elements Injectable Composition

| **Properties** | **Target** | **Justification** |
|---|---|---|
| Description | Clear, colorless, to slightly blue solution and is essentially free from visible particulates. | Based on accumulated data and as per current USP <1>. |

| Properties | Target | Justification |
|---|---|---|
| Identification | A. Zinc - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 472.215 nm when tested as directed for Procedure in the respective Assay.<br>B. Copper - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 224.700 nm when tested as directed for Procedure in the respective Assay.<br>C. Selenium - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 196.026 nm when tested as directed for Procedure in the respective Assay.<br>D. Manganese - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 279.827 nm when tested as directed for Procedure in the respective Assay. | In accordance with proposed USP monograph for Trace Elements Injectable Composition and ICH requirements for identification tests. |
| pH | Between 1.5 and 3.5 | In accordance with proposed USP monograph for Trace Elements Injectable Composition and ICH requirements for identification tests. |
| Residual Solvents | Meets Requirements under Option 2. | As per USP <467> and ICH Q3C. |
| Assay | Zinc: 90.0 % - 110.0 % Label Claim (L.C. = 3 mg/mL of Zinc) | |
| | Copper: 90.0 % - 110.0 % Label Claim (L.C. = 0.3 mg/mL of Coper) | |
| | Selenium: 90.0 % - 110.0 % Label Claim (L.C. = 60 µg/mL of Selenium) | |
| | Manganese: 90.0 % - 110.0 % Label Claim (L.C. = 55 µg/mL of Manganese) | |
| Volume of Solution | 1 mL fill: the volume is not less than the labeled volume of 1 mL. | As per USP <1151>. |
| Aluminum | Not more than 6,000 µg/L | As per 21 CFR 201.323, USP <7>, and FDA recommendation for the limit of not more than 0.6 µg/kg/day. |

| Properties | Target | Justification |
|---|---|---|
| Elemental Impurities | Meets requirements | As per ICH Q3D and USP <232> for the intended dose volume of 1 mL/day for Adult and Pediatric patients. |
| | Cadmium (Cd): Not more than 0.4 µg/mL | |
| | Lead (Pb): Not more than 0.5 µg/mL | |
| | Arsenic (As): Not more than 1.5 µg/mL | |
| | Mercury (Hg): Not more than 0.4 µg/mL | |
| | Chromium (Cr): Not more than 1.0 µg/mL | |
| | Iron (Fe): Not more than 10 µg/mL | |
| | Boron (B): Not more than 50 µg/mL | |
| | Calcium (Ca): Not more than 50 µg/mL | |
| | Magnesium (Mg): Not more than 50 µg/mL | |
| | Silicon (Si): Not more than 100 µg/mL | |
| Particulate Matter | NMT 6,000 particles ≥ 10 µm per vial<br>NMT 600 particles ≥ 25 µm per vial<br>If retested by the Microscopic Method:<br>NMT 3,000 particles ≥ 10 µm per vial<br>NMT 300 particles ≥ 25 µm per vial | As per USP <788>. |
| Sterility | If no growth is observed, the article tested meets the requirements of the test for sterility. | As per USP <71>. |
| Bacterial Endotoxins | The Endotoxin limit is not more than 50 EU/mL | As per USP <85> and the maximum daily dose of the drug product. |
| Other Requirements | It meets the requirements under Injections and Implanted Drug Products <1>. | As per USP <1>. |

**[0073]** While these injectable compositions contain little or no impurities, in some aspects, these compositions can include a chromium impurity in an amount not to exceed about 1 µg and, in other aspects, not to exceed 0.5 µg. In other instances, the injectable composition contains from about 0.0001 µg/mL to about 0.25 µg/mL of chromium. In many cases, the injectable composition of this disclosure does not contain any detectable chromium or no chromium at all.

**[0074]** In some embodiments, the chromium can be in the PN containing the trace elements composition or the trace elements composition itself in an amount of not more than about 0.15 µg/mL, 0.14 µg/mL, 0.13 µg/mL, 0.12 µg/mL, 0.11 µg/mL, 0.10 µg/mL, 0.09 µg/mL, 0.08 µg/mL, 0.07 µg/mL, 0.06 µg/mL, 0.05 µg/mL, 0.04 µg/mL, 0.03 µg/mL, 0.02 µg/mL to not more than about 0.01 µg/mL or lower. Therefore, in this embodiment, it is desirable to have no or little chromium.

**[0075]** In various embodiments, other elemental impurities, for example, lead, arsenic, cadmium, mercury iron, chromium (potential manufacturing process contaminants) and boron, calcium,

magnesium, and silicon (potential leachable elemental impurities from the drug product Type I glass vials and West elastomeric formulation 4432/50 grey stopper used as immediate packaging) have been considered.

**[0076]** Dosing recommendations for pediatric patients is based on body weight and ranges from about 0.2 mL to about 0.8 mL per day as shown in Table 3 where MDD refers to maximum daily dose.

**[0077]** Table 3 - Dosing Requirements in mL/kg Body Weight for Trace Element Compositions

| **Patient Group** | **Body Weight** | **MDD (mL)** |
|---|---|---|
| Adult | ≥50 kg | 1 mL |
| Pediatric | 40 kg to 49 kg | 0.8 mL |
| Pediatric | 30 kg to 39 kg | 0.6 mL |
| Pediatric | 20kg to 29 kg | 0.4 mL |
| Pediatric | 10 kg to 19 kg | 0.2 mL |

**[0078]** In some embodiments, the permitted daily limits (PDL) of the injectable trace elements of the current application include, as little as possible of cadmium, lead, arsenic, mercury, cobalt, vanadium, nickel, thallium, gold, palladium, iridium, osmium, rhodium, ruthenium, silver, platinum, lithium, antimony, barium, molybdenum, tin, chromium, aluminum, boron, calcium, iron, potassium, magnesium, sodium, tungsten, and/or silicon.

**[0079]** In some embodiments, the permitted daily limits (PDL) of the injectable trace elements of the current application are not to exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

**[0080]** Permitted Daily Exposure (PDE) for pediatric patient groups were calculated using the following equation: PDE (µg/day) for Pediatric = PDE per ICH (µg/day)/(50 kg)(10 kg).

**[0081]** Concentration limit for each element is based on PDE, the maximum daily volume, and ICH

control threshold, defined as a level that is 30% of the established PDE in the drug product was calculated using the following formulas:

**[0082]** Concentration Limit (µg/mL) = PDE (µg/Day) / Maximum Daily Volume (mL)

**[0083]** Control Threshold (µg/mL) = Concentration Limit (µg/mL) / 100 % · 30 %

**[0084]** A summary of PDEs, concentration limits, and 30% control thresholds for evaluated elements are provided in Table 4.

**[0085]** Table 4 - Elemental Impurities Concentration Limits for Trace elements injectable composition, USP for Pediatric Patient Population

| **Element** | **Class** | **PDE Limit** (µg/day) | **PDE Limit Pediatric** (µg/day) | **Concentration Limit** (µg/mL) | **American Regent Specification** (µg/mL) | **Control Threshold** (µg/mL) |
|---|---|---|---|---|---|---|
| **Cd** (Cadmium) | 1 | 2 | 0.4 | 0.4 | 0.4 | 0.12 |
| **Pb** (Lead) | 1 | 5 | 1 | 1 | 0.5 | 0.3 |
| **As** (Arsenic) | 1 | 15 | 3 | 3 | 1.5 | 0.45 |
| **Hg** (Mercury) | 1 | 3 | 0.6 | 0.6 | 0.4 | 0.1 |
| **Co** (Cobalt) | 2A | 5 | 1 | 1 | 1 | 0.3 |
| **V** (Vanadium) | 2A | 10 | 2 | 2 | 2 | 0.6 |
| **Ni** (Nickel) | 2A | 20 | 4 | 4 | 4 | 1.2 |
| **Tl** (Thallium) | 2B | 8 | 1.6 | 1.6 | 1.6 | 0.5 |
| **Au** (Gold) | 2B | 100 | 20 | 20 | 20 | 6 |
| **Pd** (Palladium) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Ir** (Iridium) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Os** (Osmium) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Rh** (Rhodium) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Ru** (Ruthenium) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Ag** (Silver) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Pt** (Platinum) | 2B | 10 | 2 | 2 | 2 | 0.6 |
| **Li** (Lithium) | 3 | 250 | 50 | 50 | 50 | 15 |
| **Sb** (Antimony) | 3 | 90 | 18 | 18 | 18 | 5.4 |
| **Ba** (Barium) | 3 | 700 | 140 | 140 | 140 | 42 |
| **Mo** (Molybdenum) | 3 | 1,500 | 300 | 300 | 300 | 90 |
| **Sn** (Tin) | 3 | 600 | 120 | 120 | 120 | 36 |
| **Cr** (Chromium) | 3 | 1,100 | 220 | 1.0 | 1.0 | 0.3 |
| **Al** (Aluminum) | other | 6 | 6 | 6 | 6.0 | 1.88 |
| **B** (Boron) | other | 3,400 | 680 | 50 | 50 | 15 |
| **Ca** (Calcium) | other | 82,500 | 16,500 | 50 | 50 | 15 |
| **Fe** (Iron) | other | 1,300 | 260 | 10 | 10 | 3 |
| **K** (Potassium) | other | 470,000 | 94,000 | 94,000 | 94,000 | 28,200 |
| **Mg** (Magnesium) | other | 35,000 | 7,000 | 50 | 50 | 15 |
| **Na** (Sodium) | other | 120,000 | 24,000 | 24,000 | 24,000 | 7,200 |

| Element | Class | PDE Limit (µg/day) | PDE Limit Pediatric (µg/day) | Concentration Limit (µg/mL) | American Regent Specification (µg/mL) | Control Threshold (µg/mL) |
|---|---|---|---|---|---|---|
| **W** (Tungsten) | other | N/A | N/A | N/A | 1 | 1 |
| **Si** (Silicon) | In-house | 19,200 | 3,840 | 100 | 100 | 30 |

**[0086]** In various embodiments, the trace elements injectable compositions of this application do not contain any detectable chromium or any chromium at all. However, in other embodiments, for example, in a selenious acid injection or zinc sulfate injection or even in an injectable composition containing zinc, copper, selenium and manganese, the chromium content will not exceed about 0.3 µg/mL.

**[0087]** In various embodiments, the injectable compositions of this application also include (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7 mcg/kg/day, aluminum from about 0.0001 to about 0.6 mcg/kg/day or a mixture thereof; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7 mcg/kg/day, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof. In other embodiments, the injectable composition of this application also includes (i) iron from about 0.0001 to about 10 µg/mL, silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron from about 0.0001 to about 50 µg/mL or a mixture thereof; or (ii) iron from about 0 to about 10 µg/mL, silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof.

pH Considerations

**[0088]** In various aspects, the injectable composition described in this application has a pH of from about 1.0 to about 5. In other aspects, the injectable composition has a pH from about 1.5 to about 3.5 or from about 1.5 to about 4.0. In many aspects, the pH of the trace elements composition described in this application can vary from about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9. 5.0. In some instances, sodium hydroxide or sulfuric acid can be added to adjust the pH.

**[0089]** In some embodiments, pH limits for multi-element and/or single entity trace elements injections are listed in Table 5 below.

**[0090]** Table 5 - pH Limits for Multi-Element and Single Entity Trace Elements Injections

| Drug Product | Fill size | Container | USP pH limit | In-process pH limit |
|---|---|---|---|---|
| Trace elements injectable composition, USP (3 mg/mL Zn as zinc sulfate, 0.3 mg/mL Cu as cupric sulfate, 55µg/mL Mn as manganese sulfate, 60 µg/mL Se as selenious acid) | 1 mL | 2 mL vial | 1.5 to 3.5 | 1.9 to 2.1 |
| Zinc Sulfate Injection, USP 3 mg/mL (3 mg/mL Zn as zinc sulfate)<br>Zinc Sulfate Injection, USP 5 mg/mL (5 mg/mL Zn as zinc sulfate) | 10 mL<br>5 mL | 10 mL vial<br>5 mL vial | 2.0 to 4.0 | 2.2 to 2.5 |
| Selenious Acid Injection, USP | 10 mL | 10 mL vial | 1.8 to 2.4 | 2.0 to 2.2 |

**[0091]** With the exception of selenious acid, the active ingredients in trace elements injectable compositions of this application, are formed from their specific trace elements (zinc, copper, and manganese) by reaction with acids (sulfuric acid or hydrochloric acid) to form their respective mineral salt (e.g., zinc sulfate, cupric sulfate, and manganese sulfate). As weak acids, these salts are more stable in acidic solutions because in neutral and alkaline solutions they form metal hydroxides (e.g., $Zn(OH)_2$; $Cu(OH)_2$; and $Mn(OH)_2$) which may precipitate. In the case of selenious acid, to maintain the active ingredient in the ionized form, a low pH is recommended.

**[0092]** The compositions of this application can be at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition designed to be injected or added to a parenteral nutrition. However, in some embodiments, the compositions can comprise a preservative. The preservative can be, in some cases, benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

**[0093]** The injectable composition of trace elements can be dispensed in single dose vial or can be dispensed in multi-dose vials. The trace elements composition of this application is often presented as a 1-mL fill in a 2-mL single dose preservative free vial. In many instances the vial can accommodate from about be 1 mL, 2, 3, 4, 5, 6, 7, 8, 9 to about 10 mL of fluid. In some cases, the vials can be prepared of Pyrex glass or have the inside surface sprayed or coated with silica or can be made of plastic material. This is to minimize the amount of aluminum that may potentially be leaching from a glass

vial to an amount not to exceed 0.6 µg/kg of body weight of a patient in need of trace elements treatment or no more than 25 µg/L of intravenous (IV) infusion. In some cases, the amount of aluminum can vary from about 1 µg/mL (1 ppm) to about 6 µg/mL of aluminum. In other cases, there is no aluminum present.

**[0094]** In some embodiments, the injectable compositions comprising water, from about 900 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition and can be used as a component of or additive to a parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof. In other embodiments, the injectable compositions comprise water, from about 2000 µg to about 4,000 µg of zinc, from about 200 µg to about 400 µg of copper, from about 30 µg to about 90 µg of selenium, and from about 20 µg to about 80 µg of manganese per 1 mL of the injectable composition and can be used as a component of or additive to a parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof.

**[0095]** The parenteral nutrition (PN) can include at least one of an amino acid, dextrose, a lipid, an electrolyte, or a mixture thereof. The at least one of (i) the amino acid comprises lysine hydrochloride, phenylalanine, leucine, valine, threonine, methionine, isoleucine, tryptophan, alanine, arginine, glycine, proline, histidine, glutamic acid, serine, aspartic acid, tyrosine or a mixture thereof; (ii) the dextrose comprises dextrose monohydrate; (iii) the lipid comprises soybean oil, phospholipid, glycerin or a mixture thereof; or (iv) the electrolyte comprises sodium acetate trihydrate, potassium chloride, sodium chloride, potassium acetate, sodium glycerophosphate anhydrous, magnesium sulfate heptahydrate, calcium chloride dihydrate, calcium gluconate or a mixture thereof. The resulting parenteral nutrition (PN) compositions can have a pH in a range from about 3.5 to about 7.9.

**[0096]** The injectable PN compositions described in this disclosure are also nonpyrogenic solutions. Unexpectedly, it has been found that including trace elements in a parenteral nutrition allowed the parenteral nutrition to be stable when stored from about 2 ºC to about 8 ºC for at least up to about 14 days. In some instances, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition can maintain a pH from about 5.50 to about 5.90. Moreover, in other instances, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm.

**[0097]** In some embodiments, the parenteral nutrition can be in solution form and contains 0.2 mL to 1 mL trace elements injection per liter, can have no or negligible amounts of aluminum, for example, from about 0.2 µg/mL to about 6 µg/mL, which is an amount that should not be exceeded. In other cases, there is no aluminum present, which is therefore absent.

**[0098]** In many embodiments, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition does not exhibit microbial growth. Microbes that could otherwise grow in the parenteral nutrition composition include *S. aureus, P. aeruginosa, E. coli, C. albicans, A. brasiliensis* or a mixture thereof. As with other compositions described in this application, parenteral nutrition compositions including trace elements are dispensed in a container typically is from about a 50 mL container to about a 4000 mL container. The parenteral nutrition can be in glass, polyvinyl chloride, di(2-ethylhexyl) phthalate, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polyolefin or a combination thereof that can hold larger volume parenteral nutrition from about a 50 mL container to about a 4000 mL. The parenteral nutrition container can have at least one port for the injection of the trace elements and/or other additives into the parenteral nutrition container.

**[0099]** The trace elements, before being added to the parenteral nutrition, can be in a single use vial or an ampule or in a container which comprises a vial having a stopper acceptable for a parenteral drug product and/or a cap. In many aspects, the trace elements can be placed into a 1mL single dose vial or in 10 mL multiple dose vial. The vial or ampules can be made of molded glass, glass coated with silica or polypropylene.

Parenteral Nutrition Compositions Containing Trace Elements

**[00100]** Parenteral nutrition refers to solutions for the intravenous administration of nutrients necessary for the maintenance of life. Parenteral nutrition can be prepared not only for adult patients but also for pediatric and/or neonatal patients.

**[00101]** An injectable parenteral nutrition containing trace elements is provided that is stable for a longer period of time, thereby reducing the time and costs associated with frequent admixing. The quality of life of the patient and the caregiver is also improved by avoiding frequent trips to healthcare facilities for the admixing of injectable parenteral nutrition. An injectable parenteral nutrition containing trace elements is also provided that can be made in daily doses or in batches because it is stable for a longer period of time.

**[00102]** For example, because the PN containing one or more trace elements of the current application has been found to be stable under refrigeration for up to 14 days, now the healthcare provider (e.g., pharmacist) can make the daily dose of parenteral nutrition in batches for one or more patients and, for example, a week supply or more can be admixed and dispensed for that particular patient, which eliminates the need and reduces costs as now that pharmacist will not need to be available on a daily basis to make the parenteral nutrition close in time to when it is administered to the patient. Further, less frequent trips back and forth to the healthcare facility are required.

**[00103]** One or more trace elements can be added to the amino acids, dextrose, lipids, and/or electrolytes in the parenteral nutrition. The amino acids, dextrose, lipids, and/or electrolytes in the parenteral nutrition can be from commercially available parenteral nutrition products, such as for example, AminoProtect® (essential and non-essential amino acids, Anazao Health Corp.), Aminosyn® II (amino acid injection with electrolytes in dextrose injection with calcium, Hospira, Inc.), Aminosyn® II/Electrolytes (amino acid injection with electrolytes in dextrose injection with calcium, Hospira Inc.), Aminosyn® M (a crystalline amino acid solution with electrolytes, Hospira Inc.), Aminosyn® (a crystalline amino acid solution with electrolytes, Hospira Inc.), Aminosyn®-HBC (sulfite-free, amino acid injection high branched chain, Hospira Inc.), Aminosyn®-PF (sulfite-free, amino acid injection — pediatric formula, Hospira Inc.), Aminosyn®-RF (sulfite free amino acid injection 5.2% renal formula, Hospira Inc.), Aminosyn®/Electrolytes (these are essential and non-essential amino acid injection with electrolytes, Hospira Inc.), BranchAmin® (branched chain amino acid solution of essential amino acids isoleucine, leucine, and valine, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 2.75/10, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 2.75/5, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 4.25/10, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 4.25/25, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 4.25/5, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 5/15, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 5/20, Baxter Healthcare Corp.), Clinimix® E/Dextrose (amino acid/dextrose 5/25, Baxter Healthcare Corp.), Clinimix® N14G30E (amino acid solution with electrolytes and a glucose solution with calcium, Baxter Healthcare Corp.), Clinimix® N9G15E (amino acid solution with electrolytes and a glucose solution with calcium chloride, Baxter Healthcare Corp.), Clinimix® N9G20E (amino acid solution 2.75% with electrolytes in dextrose 10% solution for injection, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 2.75/5, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose

4.25/10, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 4.25/20, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 4.25/25, Baxter Healthcare Corp.) , Clinimix®/Dextrose (amino acid/dextrose 4.25/5, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 5/15, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 5/20, Baxter Healthcare Corp.), Clinimix®/Dextrose (amino acid/dextrose 5/25, Baxter Healthcare Corp.), Clinisol® SF (sulfite-free amino acid injection, Baxter Healthcare Corp.), Clinolipid® (lipid injectable emulsion, Baxter Healthcare Corp.), Delflex® (peritoneal dialysis solutions (standard and low magnesium/low calcium) of dextrose and electrolytes in water for injection, Fresenius Medical Care North America), Elcys® (cysteine hydrochloride injection, Excela Pharma Science, LLC), FreAmine® HBC (amino acid injection, B. Braun Medical Inc.), FreAmine® III (amino acid injection, B. Braun Medical Inc.), Hyperlyte® CR (multi-electrolyte concentrate, B. Braun Medical Inc.), Hepatamine® (amino acid injection, B. Braun Medical Inc.), Intralipid® (purified soybean oil, purified egg lipids and glycerol anhydrous, Baxter healthcare Corp.), Isolyte® M in dextrose (multi-electrolyte injection in 5% dextrose, B. Braun Medical Inc.), Isolyte® P in dextrose (multi-electrolyte injection in 5% dextrose, B. Braun Medical Inc.), Isolyte® S in dextrose (multi-electrolyte injection, B. Braun Medical Inc.), Kabiven® (amino acids, electrolytes, dextrose and lipid injectable emulsion, Fresenius Kabi), Liposyn® II (intravenous fat emulsion contains 5% safflower oil, 5% soybean oil, up to 1.2% egg phosphatides, Hospira, Inc.), NephrAmine® (essential amino acid injection, B. Braun Medical Inc.), Novamine® (15% amino acids injection of essential and nonessential amino acids, Hospira Inc.), Nouress® (cysteine hydrochloride injection, Avadel Legacy Pharmaceuticals, LLC), Nutrilipid® (plant based fat emulsion, B. Braun Medical Inc.), Nutrilyte® Pro (multi-electrolyte injection, American Regent Inc.), Nutrilyte® II (multi-electrolyte injection, American Regent Inc.), Omegaven® (fish oil triglycerides, Fresenius Kabi), Perikabiven® (amino acids, electrolytes, dextrose and lipid injectable emulsion, Fresenius Kabi USA, LLC), Plasma-Lyte® 56 (multiple electrolytes and dextrose injection, Type 1, USP Baxter Healthcare Corporation) Plasma-Lyte 148 ® (multiple electrolytes and dextrose injection, Type 1, USP Baxter Healthcare Corporation), Procalamine® (3% amino acid and 3% glycerin injection with electrolytes, B. Braun Medical Inc.), Plenamine® (15% amino acid injection, B . Braun Medical Inc.), Premasol® (sulfite-free amino acid injection, Baxter Healthcare Corp.), Prosol® (amino acids injection, Baxter Healthcare Corp.), Renamin® (amino acid Injection, Baxter Healthcare Corp.), Ringer's injection, SMOFlipid (fish oil and plant based fat emulsion, Fresenius Kabi), Synthamin® 17 (10% amino acid infusion product, Baxter Healthcare Corp.),

Travasol® (amino acid injection for intravenous use, Baxter Healthcare Corp.), TrophAmine® (amino acid injection, B. Braun Medical Inc.), dextrose, sodium chloride, calcium chloride, potassium chloride, magnesium chloride, sodium acetate, or a combination thereof.

**[00104]** Dosing recommendations for pediatric patients is based on body weight and ranges from about 0.2 mL to about 0.8 mL per day as shown in Table 3 above, where MDD refers to maximum daily dose.

**[00105]** Parenteral nutrition has become an integral part of the support of the neonate who is either unable to receive or tolerate enteral feeding. Feeding practices are generally based on birth weight, with the smallest infants receiving parenteral nutrition for the longest time after birth. Generally, neonates include infants in the first four weeks after birth. Term neonates have an estimated weight of from about 3 kg to less than 5 kg and preterm neonates have an estimated weight of less than 3 kg. Neonates also include very low birth weight (those having a weight of less than 1500 g) and extremely low birth weight (those having a weight of less than 1000 g). These neonate infants are susceptible to growth failure in postnatal life if nutritional demands are not met. Poor postnatal growth in preterm infants is associated with adverse neurodevelopmental outcomes during childhood. Thus, early parental nutrition is of paramount importance to provide appropriate protein and energy in neonates, both preterm and term, when enteral nutrition is not feasible or is suboptimal. We have, therefore, prepared a stable parenteral nutrition that can be used in a wide spectrum of patients, adult, pediatric and neonate.

**[00106]** The nutrient components of PN include dextrose, amino acids, fat, electrolytes, multivitamins, trace elements and water. Regarding the content and amounts of multivitamins and trace elements in PN solutions or compositions compliance with recommendations by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is followed. In accordance with A.S.P.E.N. recommendations, an injectable composition is provided which is a parenteral nutrition. The parenteral nutrition or parenteral nutrition composition of this application comprises at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof and a trace element component which comprises, consists essentially of or consists of at least one of zinc, copper, selenium, and manganese. This means that, in some cases, the parenteral nutrition contains only one of the trace elements, for example only zinc or copper or manganese or selenium. In other cases, the parenteral nutrition can include more than one trace element, for example, only zinc and copper or a mixture of all four of these elements.

**[00107]** In various embodiments, before any trace elements compositions are added to the parenteral nutrition, the parenteral nutrition can comprise trace amounts of zinc, copper, manganese, and

chromium from other sources, for example water for injection and/or the container of the injectable composition. For example, in some cases, the parenteral nutrition can comprise inherently and/or as impurities zinc in an amount of less than about 750 µg/L, copper in an amount of less than 75 µg/L, selenium in an amount of less than 15 µg/L, manganese in an amount of less than 13.7 µg/L and chromium in an amount of less than 0.25 µg/mL.

**[00108]** In various aspects, the parenteral nutrition comprises, consists essentially of or consists of from about 900 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition. In some embodiments, the parenteral nutrition comprises, consists essentially of, or consists of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition. In other embodiments, the parenteral nutrition comprises, consists essentially of, or consists of 1,000 µg of zinc, 60 µg of copper, 6 µg of selenium, and 3 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition.

**[00109]** The elemental zinc can be provided by zinc sulfate or zinc heptahydrate. Copper can be provided by cupric sulfate or cupric sulfate pentahydrate. Manganese can be sourced from manganese sulfate or manganese sulfate monohydrate. Selenium can be provided by selenious acid. Thus, in many cases, in the parenteral nutrition, zinc comprises zinc sulfate or zinc sulfate heptahydrate in an amount of from about 13.1 mg to about 13.3 mg, copper comprises, consists essentially of or consists of cupric sulfate or cupric sulfate pentahydrate in an amount of from about 1.1 mg to about 1.2 mg, manganese comprises manganese sulfate or manganese sulfate monohydrate in an amount of from about 0.16 mg to about 0.18 mg and selenium comprises selenious acid in an amount of from about 95 µg to about 99 µg per about 250 mL to 4000 mL of parenteral nutrition.

**[00110]** In some embodiments, in the parenteral nutrition, the zinc sulfate or zinc sulfate heptahydrate comprises, consists essentially of, or consists of an amount of about 13.2 mg, the cupric sulfate or the cupric sulfate pentahydrate comprises, consists essentially of or consists of an amount of about 1.179 mg, the manganese sulfate or manganese sulfate monohydrate comprises, consists essentially of or consists of an amount of about 0.0169 mg and the selenious acid comprises, consists essentially of or consists of an amount of about 98 µg.

**[00111]** In some embodiments, each trace element can be added to a PN solution, one at a time and the injection composition of this application can contain only one of these trace elements, for example, only zinc, copper, manganese, or selenium. This approach allows for tailoring of a PN solution to the

needs of a specific patient in need who might have a zinc deficiency only, for example, but is not deficient in copper, manganese, or selenium.

**[00112]** In some embodiments, a selenious acid injection, USP can be indicated for use as a supplement to intravenous solutions given for parenteral nutrition (PN). Administration of selenium in PN solutions helps to maintain plasma selenium levels and to prevent depletion of endogenous stores and subsequent deficiency symptoms. Each mL contains 98.0 µg of selenious acid, USP (equivalent to 60 µg of elemental selenium), nitric acid, national formulary (NF) for pH adjustment (1.8 to 2.4) and water for injection, USP quantity sufficient (q.s). In some embodiments, the trace element composition comprises selenium or selenious acid and has a pH of about 3.5 to about 7.9.

**[00113]** In many aspects, selenium is present in the same concentration of 60 µg of elemental selenium per mL in the injectable composition comprising beside selenium, the multi-trace product which contains zinc sulfate heptahydrate 13.20 mg (equivalent to 3 mg zinc), cupric sulfate pentahydrate 1.18 mg (equivalent to 0.3 mg copper), and manganese sulfate monohydrate 169 µg (equivalent to 55 µg manganese) sulfuric acid for pH adjustment and water for injection q.s. Since selenious acid injection, USP could be administered in parenteral solutions as both, single and a component of multi-trace solutions, it was deemed appropriate to utilize the study of the trace elements injection which also contains zinc, copper and manganese USP for selenious acid injection, USP.

**[00114]** In many aspects, the parenteral nutrition includes at least one of (i) the amino acid which comprises lysine hydrochloride, phenylalanine, leucine, valine, threonine, methionine, isoleucine, tryptophan, alanine, arginine, glycine, proline, histidine, glutamic acid, serine, aspartic acid, tyrosine or a mixture thereof; (ii) the dextrose which comprises dextrose monohydrate; (iii) the lipid which comprises soybean oil, phospholipid, glycerin or a mixture thereof; (iv) the electrolyte which comprises sodium acetate trihydrate, potassium chloride, sodium chloride, potassium acetate, sodium glycerophosphate anhydrous, magnesium sulfate heptahydrate, calcium chloride dihydrate, calcium gluconate or a mixture thereof and (v) water, generally water for injection. In various aspects, the parenteral nutrition solution is nonpyrogenic.

**[00115]** In various aspects, the parenteral nutrition has a pH that varies is from about 3.5 to about 7.9. In some cases, the pH can be from about 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.3, 5.5., 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8 to about 7.9.

**[00116]** It has been surprisingly found that when stored from about 2 ºC to about 8 ºC for up to about 14 days, the parenteral nutrition which includes the trace element composition of this application is stable remaining in a state or condition that is suitable for administration to a patient and without undergoing a substantial change in the potency of the active agent in the formulation over this specified time period.

**[00117]** Further, when stored from about 2 ºC to about 8 ºC for about 14 days the parenteral nutrition maintained a pH from about 5.50 to about 5.90. When stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral composition of this application comprises, consists essentially of or consists of at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm. Moreover, when the parenteral nutrition of this disclosure is stored from about 2 ºC to about 8 ºC for about 14 days, it was surprisingly found that it did not exhibit any significant microbial growth with respect to such microbes as *S. aureus, P. aeruginosa, E. coli, C. albicans, A. brasiliensis* or a mixture thereof.

**[00118]** Generally parenteral nutrition can be prepared in a dual or triple chamber infusion bag which can have a separate port for the addition of trace elements prior to administration. Aluminium (Al) toxicity in parenteral nutrition solutions (PNS) has been a problem for many patients with impaired kidney function who frequently are in need of parenteral nutrition. In accordance with 21CFR201.323 (revised as of April 1, 2019), regarding aluminum content, the Federal Drug Administration prescribes that the parenteral nutrition solution must contain a warning that the solution contains no more than 25 mcg/L of aluminum which may reach toxic levels with prolonged administration in patients with renal impairment. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Patients with renal impairment, including preterm infants, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day, accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Nevertheless, whether or not the parenteral nutrition of this disclosure includes the trace elements composition as a component, the amount of aluminum should be kept in a daily exposure amount from about 0.1 µg/kg, 0.2, 0.3, 0.4, 0.5 to about 0.6 µg/kg, in any event not to exceed 0.6 µg/kg. In many cases, the parenteral nutrition of this application does not contain any aluminum and/or chromium as impurities.

**[00119]** In some embodiments, parenteral nutrition includes multivitamins, such as for example, vitamins, A, D, E, C, B1, B2, B6, B12, niacinamide, dexpanthenol, biotin and/or folic acid. In other

embodiments, the trace elements when added to the PN may interact with the vitamins in the PN and may cause precipitation. Thus, in some embodiments, the injectable composition containing trace elements is added to parenteral nutrition that does not contain any vitamins.

**[00120]** In some embodiments, to the parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof and a trace element, one or more injectable vitamins can be added. These one or more injectable vitamins can be added individually or together to the parenteral nutrition. These vitamins include one or more of vitamin A (e.g., retinol), vitamin D (e.g., ergocalciferol), vitamin E (e.g., dl-alpha-tocopheryl acetate), vitamin K (e.g., phytonadione), vitamin C (e.g., ascorbic acid), niacinamide, vitamin B2 (e.g., as riboflavin 5-phosphate sodium), vitamin B1 (e.g., thiamine), vitamin B6 (e.g., pyridoxine HCl), dexpanthenol (e.g., d-pantothenyl alcohol), biotin, folic acid, B12 (e.g., cyanocobalamin), or a combination thereof.

**[00121]** An example of vitamins for injection for adults (INFUVITE® Adult) that can be added to the parenteral nutrition before or after the addition of the trace elements include those vitamins in a two vial system listed below.

| Vial 1* | |
|---|---|
| Fat Soluble Vitamins** | |
| Ingredient | Amount per Unit Dose |
| Vitamin A (retinol) | 1 mg[a] |
| Vitamin D (ergocalciferol) | 5 mcg[b] |
| Vitamin E (dl-alpha-tocopheryl acetate) | 10 mg[c] |
| Vitamin K (phytonadione) | 150 mcg |
| Water Soluble Vitamins | |
| Vitamin C (ascorbic acid) | 200 mg |
| Niacinamide | 40 mg |
| Vitamin B2 (as riboflavin 5-phosphate sodium) | 3.6 mg |
| Vitamin B1 (thiamine) | 6 mg |
| Vitamin B6 (pyridoxine HCl) | 6 mg |
| Dexpanthenol (d-pantothenyl alcohol) | 15mg |

* With 30% propylene glycol and 2% gentisic acid ethanolamide as stabilizers and preservatives; sodium hydroxide for pH adjustment; 1.6% polysorbate 80; 0.028% polysorbate 20; 0.002% butylated hydroxytoluene; 0.0005% butylated hydroxyanisole.

** Fat soluble vitamins A, D, E and K are water solubilized with polysorbate 80.

(a) 1 mg vitamin A equals 3,300 USP units.

(b) 5 mcg ergocalciferol equals 200 USP units.

(c) 10 mg vitamin E equals 10 USP units.

| Vial 2* | |
|---|---|
| Biotin | 60 mcg |
| Folic acid | 600 mcg |
| B12 (cyanocobalamin) | 5 mcg |

* With 30% propylene glycol; and citric acid, sodium citrate, and sodium hydroxide for pH adjustment.

**[00122]** An example of pediatric injectable vitamins that can be added to the parenteral nutrition before or after the addition of the trace elements include those found in INFUVITE® PEDIATRIC

Each 4 mL of Vial 1 contains 10 vitamins (shown below).

Active Ingredients in 4 mL of Vial 1

| Active Ingredient | Quantity |
|---|---|
| Ascorbic acid (Vitamin C) | 80 mg |
| Vitamin A* (as palmitate) | 2,300 IU (equals 0.7 mg) |
| Vitamin D3* (cholecalciferol) | 400 IU (equals 10 mcg) |
| Thiamine (Vitamin B1) (as the hydrochloride) | 1.2 mg |
| Riboflavin (Vitamin B2) (as riboflavin 5-phosphate sodium) | 1.4 mg |
| Pyridoxine HCl (Vitamin B6) | 1 mg |
| Niacinamide | 17 mg |
| Dexpanthenol (as d-pantothenyl alcohol) | 5mg |
| Vitamin E* (dl-α-tocopheryl acetate) | 7 IU (equals 7 mg) |
| Vitamin K1* | 0.2 mg |

*Polysorbate 80 is used to water solubilize the oil-soluble vitamins A, D, E, and K.

Inactive ingredients in Vial 1: 50 mg polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment, and water for injection. Each 1 mL of Vial 2 contains 3 vitamins (see shown below).

Active Ingredients in 1 mL of Vial 2

| Active Ingredient | Quantity |
|---|---|
| Folic acid | 140 mcg |
| Biotin | 20 mcg |
| Vitamin B12 (cyanocobalamin) | 1 mcg |

Inactive ingredients in Vial 2: 75 mg mannitol, citric acid and/or sodium citrate for pH adjustment and water for injection.

Container of the Trace Elements Injectable Composition

**[00123]** In various embodiments, the injectable composition containing trace elements is disposed in a container. The container can have a variety of volumes. Typically, the container for the trace elements injectable composition before it is added to a parenteral solution can have a volume of from about 1 mL to about 10 mL. In some examples, the container can have a volume of from about 1 mL, 2, 3, 4, 5, 6, 7, 8, 9 to about 10 mL.

**[00124]** Containers in which the trace elements composition can be stored include any container that is suitable for storing a pharmaceutical. Typical containers can be inert to the trace elements composition. In some embodiments, treated glass containers such as siliconized glass containers are also useful. In some embodiments, plastic containers can also be used that are inert and/or are treated or coated to be inert. Suitable containers include vials, ampules, bottles, cartridges, syringes, pre-filled syringes, plastic IV bags, or the like. The container can be sealed with a closure, such as, for example, a rubber stopper, plunger, lid, top or the like. Suitable inert or non-reactive stoppers may be obtained from several commercial manufacturers. In general, the closures can be made with inert, non-reactive materials with little to no leachables. In some embodiments, closures also include those that are coated or treated with inert materials such as siliconized polymer or Teflon/fluoropolymer coated/treated closures. By way of example and not in limitation of the present application, rubber closures that are suitable in the present application include bromobutyl rubber, chlorobutyl rubber, fluoropolymers, silicones, siliconized bromobutyl rubber, and/or siliconized chlorobutyl rubber.

**[00125]** Non-reactive, non-elastomeric closures are also useful for the trace elements composition. For example, non-rubber closures include metal closures, or plastics such as polyethylene,

polypropylene, nylon, polyurethane, polyvinylchloride, polyacrylates, polycarbonates, or the like that cause little to no degradation to the trace elements composition or that are treated or coated so as to cause little or no degradation of the trace elements composition.

**[00126]** In many aspects, useful containers for the injectable compositions of this disclosure include a single use vial or ampule or the containers comprise a vial having a barrier coated stopper and/or an aluminum cap. In some embodiments, the vial or ampule comprises molded glass or polypropylene. In other cases, the container for the injectable compositions of this disclosure can be made of a variety of materials. Non-limiting materials can include glass, a plastic (e.g., polyethylene, polypropylene, polyvinyl chloride, polycarbonate, etc.), the like, or a combination thereof provided that it can both prevent oxygen penetration and minimize aluminum, heavy metals and anions contamination to the composition. In certain embodiments, the container is fabricated from multilayered plastic (PL 2501, PL 2040), also known as a galaxy container, a plastic container primarily for intravenous use. Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period.

**[00127]** In other aspects, the container can be fabricated from glass as a single use 1 mL vial, for example, a Type I glass vial for injectable products. In some aspects, the pharmaceutical compositions of this disclosure can also be stored in glass vials or ampules, for example, single use 1 mL glass vials or ampules. In various embodiments, the container can be Type I glass (e.g., molded glass, tubing glass, glass coated with silica, etc.), plastic (e.g., polymeric materials such as polypropylene, COC, COP, multi-shell, etc.) or the like. In some embodiments, Type I glass can be a borosilicate glass, which is relatively inert with good chemical resistance.

**[00128]** In some cases, the injectable composition is dispensed into a container that can be a single use container, for example, a single use vial or ampule or the container comprises a vial having a barrier coated stopper and/or an aluminum cap. As described above, the vial or ampule can be made of molded glass or polypropylene. The container may, optionally, further comprise a light barrier. In certain embodiments, the light barrier can be an aluminum material disposed over a pouch.

**[00129]** The injectable composition of trace elements can be dispensed, for example, in 1mL single dose vial or can be dispensed in 10 mL multi-dose vials. In some cases, the vials can be prepared of Pyrex glass or sprayed or coated with silica or can be made of plastic material. This is to minimize the amount of aluminum that may potentially be leaching from a glass vial to a daily exposure amount not to exceed 0.6 μg/kg of body weight of a patient in need of trace elements treatment or no more than 25

µg/L of intravenous (IV) infusion for parenteral nutrition. In some cases, the daily exposure amount of aluminum can vary from about 0.1 µg/kg to about 0.6 µg/kg of aluminum. In other cases, there is no detectable aluminum present in the injectable compositions of this application.

**[00130]** To ensure that the amount of aluminum in a multi-component PN is maintained below 25 µg/L (CFR 201.323), choosing a low aluminum content vial such as Gerresheimer Gx®33 is expected to reduce the amount of aluminum leached from a glass container. The West 4432 FluroTec® B2-40 coated stopper was selected because the barrier technology of the FluroTec® film, in combination with the B2-40 coating, utilized in the West 4432 FluroTec® B2-40 stopper can significantly reduce potential sources of particulate contamination, specifically by reducing inorganic and organic leachable substances and by providing lubricity without the need for free silicone oil. Using glass vials with or without a coated stopper provided a targeted shelf-life of 24 months.

**[00131]** The container in which the injectable compositions are held may affect the level of certain components. In certain embodiments, the injectable composition can be enclosed in a single-use container. These containers can include, for example, vials, ampules, or syringes. As previously discussed, the pH range for the injectable composition of either parenteral nutrition and/or injectable composition comprising trace elements varies from about 1.0 to about 7. This pH may disrupt the plastic coating or silicon coating inside the glass container and aluminum, heavy metals and anions could leach during the shelf life of the product, especially over prolonged storage of the product.

**[00132]** Elemental impurities monitored in the finished drug products described in this disclosure include without limitation Cd, Pb, As, Hg, Co, V, Ni, Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt, Li, Sb, Ba, Mo, Cu, Sn, and Cr. In some embodiments, the injectable composition comprising trace element or the parenteral nutrition comprising the injectable composition include 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, to about 5.0 ppb of these impurities. However, the levels of specific metals ions are monitored in the finished drug product units over the entire shelf life but are not quantified in the bulk Water for Injection (WFI), USP used to prepare the batch. Rather, the level of soluble metals and any other electrolytes is measured in the bulk WFI, USP via measurement of conductivity.

**[00133]** In some embodiments, the one or more trace elements are indicated for use as a supplement to intravenous solutions given for parenteral nutrition. Administration of the solution in parenteral TPN solutions helps to maintain plasma levels of one or more elements: zinc, copper, manganese, selenium or optionally

chromium and to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms. In some embodiments, the one or more trace elements can be used to maintain, supplement or increase one or more trace elements: zinc, copper, manganese, selenium or optionally chromium.

**[00134]** The trace element can be elemental and sourced from any salt, hydrate, and/or solvate forms thereof. For example, the elemental zinc can be from, for example, zinc gluconate trihydrate, zinc gluconate, zinc chloride, zinc sulfate, zinc sulfate heptahydrate, zinc oxide, zinc sulfide, zinc trisodium, zinc carbonate, zinc acetate, zinc citrate, zinc lactate, zinc hydroxide or a combination thereof. For example, the elemental manganese can be from, for example, manganese sulfate, manganese sulfate monohydrate, manganese chloride, manganese gluconate, manganese glycerophosphate, manganese carbonate, manganese hydroxide, or a combination thereof. For example, the elemental copper can be from, for example, cupric sulfate, cupric sulfate pentahydrate, cupric hydroxide, cupric oxide, copper carbonate, copper citrate, copper gluconate, or a combination thereof. For example, the elemental selenium can be from, for example, selenious acid, sodium selenite, disodium selenite, sodium hydrogen selenite, potassium selenite, zinc selenite, copper selenite, manganese selenite or a combination thereof. In some embodiments, the zinc selenite, copper selenite, or manganese selenite or a combination thereof are not readily soluble in water but at a pH of between about 1.5 to about 3.5, the zinc selenite, copper selenite, or manganese selenite or a combination are water soluble. For example, the elemental chromium can be from, for example, chromium trichloride, chromium trichloride hexahydrate, chromium trisulfate or a combination thereof.

**[00135]** The trace elements can be in the trace elements composition in the following ratios:

| Product | Ratio elemental Zn to elemental Cu | Ratio elemental Zn to elemental Mn | Ratio elemental Zn to elemental Se |
|---|---|---|---|
| MTE-4® | 1 mg Zn to 0.4 mg Cu Ratio: 2.5 to 1 | 1 mg Zn to 0.1 mg Mn Ratio: 10 to 1) | N/A |
| MTE-4® Conc. | 5 mg Zn to 1 mg Cu Ratio: 5 to 1 | 5 mg Zn to 0.5 mg Mn Ratio: 10 to 1 | N/A |
| MTE-4® Neonatal | 1.5 mg Zn to 0.1 mg Cu Ratio: 15 to 1 | 1.5 mg Zn to 0.025 mg Mn Ratio: 60 to 1 | N/A |
| MTE-4® Pediatric | 1 mg Zn to 0.1 mg Cu Ratio: 10 to 1 | 1 mg Zn to 0.025 mg Mn Ratio: 40 to 1 | N/A |
| MTE-5® | 1 mg Zn to 0.4 mg Cu Ratio: 2.5 to 1 | 1 mg Zn to 0.1 mg Mn Ratio: 10 to 1 | 1 mg Zn to 0.02 mg Se Ratio: 50 to 1 |
| MTE-5® Conc. | 5 mg Zn to 1 mg Cu Ratio: 5 to 1 | 5 mg Zn to 0.5 mg Mn Ratio: 10 to 1 | 5 mg Zn to 0.06 mg Se Ratio: 83.3 to 1 |

**[00136]** These ratios are elemental to elemental ratios (e.g., elemental Zn to elemental Cu, elemental Zn to elemental Mn, etc.). In some embodiments, these ratios can also be the ratios for the newer formulations that

have no or little chromium. In some embodiments, the trace elements are in a ratio of: elemental zinc to elemental copper from about 100:1, 80:1, 70:1, 60:1, 50:1, 30:1, 20:1, 15:1, 10:1, 5:1, 2.5:1 to about 2:1; elemental zinc to elemental manganese in a ratio from about 4000:1, 3,000:1, 2,000:1, 1,000:1, 500:1, 200:1, 100:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15;1, 10:1 to about 5:1; elemental zinc to elemental selenium in a ratio from about 1000:1, 500:1, 200:1, 100:1, 90:1, 85:1, 83.3:1, 80:1, 75:1, 70:1, 65:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15:1, 10:1 to about 9:1; elemental copper to elemental selenium in a ratio from about 100:1, 50:1, 20:1, 15:1, 10:1, 5:1, 3:1, 2:1, 1:1 to about 0.4:1; elemental copper to elemental manganese in a ratio from about 400:1, 300:1, 200:1, 100:1, 90:1, 85:1, 80:1, 75:1, 70:1, 65:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15:1, 10:1, 5.5:1, 5:1, 2.5:1, 2:1, 1:1 to about 0.5:1; and/or elemental selenium to elemental manganese in a ratio from about 100:1, 90:1, 75:1, 50:1, 30:1, 20:1, 10:1, 5:1, 3;1, 2:1, 1.1:1, 1:1, 0.5:1, 0.4:1 to about 0.05:1.

**[00137]** In some embodiments, the trace elements can be in the trace elements composition in the following elemental ratios: Zn/Cu: 10:1, Zn/Se: 50:1, Zn/Mn: 55:1, Cu/Se: 5:1, Cu/Mn: 5.5:1, and/or Se/Mn: 1.1:1. In some embodiments, these can lead to the trace elements composition stability and the parenteral nutrition stability.

**[00138]** Exemplary trace elements compositions for use in the current application include Multitrace®-4, available from American Regent Shirley, NY, USA.

| **Multitrace®-4** (Trace Elements Injection 4, USP) | | **Multitrace®-4 Concentrate** (Trace Elements Injection 4, USP) | | **Multitrace®-4 Concentrate** (Trace Elements Injection 4, USP) | | **Multitrace®-4 Neonatal** (Trace Elements Injection 4, USP) | | **Multitrace®-4 Pediatric** (Trace Elements Injection 4, USP) | |
|---|---|---|---|---|---|---|---|---|---|
| 10 mL Multiple Dose Vial | | 1 mL Single Dose Vial | | 10 mL Multiple Dose Vial | | 2 mL Single Dose Vial | | 3 mL Single Dose Vial | |
| (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preservative Free) | |
| Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL |
| Zinc (as Sulfate) | 1 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 1.5 mg | Zinc (as Sulfate) | 1 mg |
| Copper (as Sulfate) | 0.4 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 0.1 mg | Copper (as Sulfate) | 0.1 mg |
| Manganese (as Sulfate) | 0.1 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 25 mcg | Manganese (as Sulfate) | 25 mcg |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Chromium (as Chloride) | 4 mcg | Chromium (as Chloride) | 10 mcg | Chromium (as Chloride) | 10 mcg | Chromium (as Chloride) | 0.85 mcg | Chromium (as Chloride) | 1 mcg |
| | | | | | | | | | |
| In Water for Injection, USP | N/A | In Water for Injection, USP | N/A | In Water for Injection, USP | N/A | In Water for Injection, USP | N/A | In Water for Injection, USP | N/A |
| pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide |

**[00139]** Exemplary trace elements compositions for use in the current application can also include Multitrace®-5, available from American Regent Shirley, NY, USA.

| **Multitrace®-5** (Trace Elements Injection 5, USP) | | **Multitrace®-5 Concentrate** (Trace Elements Injection 5, USP) | | **Multitrace®-5 Concentrate** (Trace Elements Injection 5, USP) | |
|---|---|---|---|---|---|
| 10 mL Multiple Dose Vial | | 1 mL Single Dose Vial | | 10 mL Multiple Dose Vial | |
| (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preserved with 0.9% Benzyl Alcohol) | |
| Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL |
| Zinc (as Sulfate) | 1 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 5 mg |
| Copper (as Sulfate) | 0.4 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 1 mg |
| Manganese (as Sulfate) | 0.1 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 0.5 mg |

| | | | | | |
|---|---|---|---|---|---|
| Chromium (as Chloride) | 4 mcg | Chromium (as Chloride) | 10 mcg | Chromium (as Chloride) | 10 mcg |
| Selenium (as Selenious Acid) | 20 mcg | Selenium (as Selenious Acid) | 60 mcg | Selenium (as Selenious Acid) | 60 mcg |
| In Water for Injection, USP | N/A | In Water for Injection, USP | N/A | In Water for Injection, USP | N/A |
| pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid | pH | Solution may be adjusted with Sulfuric Acid |

**[00140]** Exemplary trace elements compositions that can be used in the current application can include those without chromium some listed below.

| Trace Elements Injection 3, USP (No Chromium) | | Trace Elements Injection 3, USP (No Chromium) | | Trace Elements Injection 3, USP (No Chromium) | | Neonatal Trace Elements Injection 3, USP (No Chromium) | | Pediatric Trace Elements Injection 3, USP (No Chromium) | |
|---|---|---|---|---|---|---|---|---|---|
| 10 mL Multiple Dose Vial | | 1 mL Single Dose Vial | | 10 mL Multiple Dose Vial | | 2 mL Single Dose Vial | | 3 mL Single Dose Vial | |
| (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preservative Free) | |
| Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL |
| Zinc (as Sulfate) | 1 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 1.5 mg | Zinc (as Sulfate) | 1 mg |
| Copper (as Sulfate) | 0.4 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 0.1 mg | Copper (as Sulfate) | 0.1 mg |
| Manganese (as Sulfate) | 0.1 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 25 mcg | Manganese (as Sulfate) | 25 mcg |
| | | | | | | | | | |
| In Water for Injection, USP | | N/A | | In Water for Injection, USP | | N/A | | In Water for Injection, USP | |
| pH | Solution may be adjusted with Sulfuric Acid and/or Sodium | pH | Solution may be adjusted with | pH | Solution may be adjusted with | pH | Solution may be adjusted with | pH | Solution may be adjusted with |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hydroxide | | Sulfuric Acid and/or Sodium Hydroxide | | Sulfuric Acid and/or Sodium Hydroxide | | Sulfuric Acid and/or Sodium Hydroxide | | Sulfuric Acid and/or Sodium Hydroxide |

**[00141]** Trace Elements Compositions having 4 trace elements with no chromium are shown below.

| Trace Elements 4 Injection (No Chromium) | | Trace Elements 4 Injection Concentrated (No Chromium) | | Trace Elements 4 Injection Concentrated (No Chromium) | |
|---|---|---|---|---|---|
| 10 mL Multiple Dose Vial | | 1 mL Single Dose Vial | | 10 mL Multiple Dose Vial | |
| (Preserved with 0.9% Benzyl Alcohol) | | (Preservative Free) | | (Preserved with 0.9% Benzyl Alcohol) | |
| Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL | Trace Elements | Content of Trace Elements / 1 mL |
| Zinc (as Sulfate) | 1 mg | Zinc (as Sulfate) | 5 mg | Zinc (as Sulfate) | 5 mg |
| Copper (as Sulfate) | 0.4 mg | Copper (as Sulfate) | 1 mg | Copper (as Sulfate) | 1 mg |
| Manganese (as Sulfate) | 0.1 mg | Manganese (as Sulfate) | 0.5 mg | Manganese (as Sulfate) | 0.5 mg |
| Selenium (as Selenious Acid) | 20 mcg | Selenium (as Selenious Acid) | 60 mcg | Selenium (as Selenious Acid) | 60 mcg |
| In Water for Injection, USP | N/A | In Water for Injection, USP | N/A | In Water for Injection, USP | N/A |
| pH | Solution may be adjusted with Sulfuric Acid and/or Sodium Hydroxide | pH | Solution may be adjusted with Sulfuric Acid | pH | Solution may be adjusted with Sulfuric Acid |

Headspace Oxygen

**[00142]** In certain embodiments, the trace elements further comprise within the container, headspace gas that includes oxygen in an amount of from about 0.5% v/v to about 5.0% v/v, or from about 0.5% v/v to about 4.0% v/v, or from about 0.5% v/v to about 3.5% v/v, from about 0.5% v/v to about 3.0%

v/v, or from about 0.5% v/v to about 2.5% v/v, or from about 0.5% v/v to about 2.0% v/v, or from about 0.5% v/v to about 1.5% v/v, or from about 0.5% v/v to about 1.0% v/v, or in some cases from about 0.1% v/v to about 0.5% v/v, or from about 0.1% v/v to about 0.4% v/v, or from about 0.1% v/v to about 0.3% v/v, or from about 0.1% v/v to about 0.2% v/v. For the sake of clarity and the ease of discussion and measurement, these values are taken for the injectable composition at the time of its manufacture ("time zero" data point), or during and up to 1 month from time zero. Additional time points beyond the 1 month from time zero data point may provide similar headspace oxygen levels.

**[00143]** Without wishing to be bound by a particular theory, the dissolved oxygen levels, and the head space oxygen levels within a sealed container of injectable compositions described herein may reach an equilibrium at some time point during its shelf-life. Such equilibrium may be maintained for a very short time, i.e., for a few seconds, or for a very long time, i.e., for several months. Such equilibrium may on occasion be disturbed by simple agitation. Therefore, it should be recognized that dissolved oxygen levels and headspace oxygen levels may fluctuate from one time point to another in terms of absolute numbers. However, the numbers are expected to stay within the ranges disclosed herein. Occasionally, one number (e.g., dissolved oxygen) may exceed or fall out of a certain range (e.g., from about 0.5 to about 3.0 PPM) at a 15 day time point but may fall within that range at some other time point (e.g., 30 day time point, or later). Therefore, in some aspects, the ranges, subranges, and specific data points disclosed and discussed herein are suitable for time points beyond the time zero- and 1-month time points. In one aspect, the time points could be extended to from about 2 months, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, and about 24 months.

**[00144]** In some cases, the total amount of oxygen in the sealed container may be an appropriate measure to evaluate the stability of the injectable compositions. For example, the total amount of oxygen within the container may be arrived at by adding up the amount of dissolved oxygen in the carrier and the amount of head space oxygen. These values can also be expressed independently in separate units (i.e., dissolved oxygen as ppm and head space oxygen as % v/v). An example would be that the parenteral nutrition or the injectable composition of trace elements contains a dissolved oxygen level of from about 0.0 ppm to 5.0 ppm, more specifically, from about 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, to about 5.0 ppm and a head space oxygen level of about 0.5% v/v to about 4.0% v/v. In certain embodiments, the total amount of oxygen within the container is expected to increase upon filling into vials due to the inherent

aeration of the drug product during filling (e.g., splashing). Based on what has been seen for other drug products, the dissolved oxygen in the finished units (e.g., vials) is expected to be in the range of from about 0.0 ppm to about 7.0 ppm, more specifically, from about 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 to about 7.0 ppm.

**[00145]** The amount of oxygen present in the headspace of the container can be controlled by filling the headspace with an inert gas, such as nitrogen or argon. Alternatively, the head space oxygen may be controlled by vacuum operation without using an inert gas. In another aspect, the head space oxygen may be controlled by a combination of vacuum operation and inert gas overlay. In one other aspect, the head space oxygen is controlled by repeated pulses of vacuum and inert gas overlay in tandem such that the process may start first with vacuum operation followed by inert gas overlay followed by vacuum operation. The combination of vacuum operation and inert gas overlay (or inert gas overlay and vacuum operation) is considered one pulse when both steps are used together. A typical head space control operation may comprise from one to eight pulses. Typically, there could be two, three, four, or five pulses. Each pulse could last from about one tenth of one second to five seconds or from five to fifteen seconds when conducted by automated high-speed equipment custom designed for this specific purpose. In some embodiments, the pulse may last from about 0.1 to about 2.0 seconds. In some embodiments, the pulse may last from about 0.1 to about 1.0 seconds, or from about 0.1 to about 0.4 seconds. When done using manual methods, each pulse could take up to 30-60 seconds or longer.

**[00146]** In many cases, the headspace oxygen of the containers useful for the injectable compositions of this disclosure include (i) from about 0.5% v/v to about 5.0% v/v from the time of manufacture to about 6 months from manufacture when stored at temperatures from 25 ºC to 60 ºC or (ii) from about 0.5% v/v to about 10.0% v/v from the time of manufacture to about 6 months from manufacture when stored at temperatures from 25 ºC to 60 ºC; and the dissolved oxygen present in the injectable composition can be in an amount from about 0.1 parts per million (ppm) to about 9 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature, wherein the composition is enclosed in a single-use container having a volume of from about 1 mL to about 10 mL.

**[00147]** During a manufacturing process, in one embodiment, dissolved oxygen levels are controlled via sparging with an inert gas. Additionally, a blanket of inert gas (e.g., nitrogen, argon, helium) can be maintained throughout manufacturing and storage to control atmospheric oxygen exposure, while

an opaque container (stainless steel or amber glass) is selected to protect the formulation from exposure to light. In some embodiments, it was found that the trace elements injectable composition of this application containing at least one of zinc, copper, manganese and selenium or a mixture thereof, a USP injectable product, was not sensitive to oxygen and thus, a nitrogen blanket/sparging during compounding was not required during the manufacturing of the trace elements injectable composition.

**[00148]** In some embodiments, the injectable composition is preservative-free. As used herein, preservative-free includes compositions that do not contain any preservative. Thus, the composition does not contain, for example, benzalkonium chloride, methyl, ethyl, propyl or butylparaben, benzyl alcohol, phenylethyl alcohol, or benzethonium.

**[00149]** In some embodiments, one or more preservatives can be incorporated into the injectable pharmaceutical composition described in this disclosure, especially in a multi-dose injectable composition. Preservatives can be introduced into a pharmaceutical solution to kill bacteria, yeast, and mold. The bacteria, yeast, and mold can be introduced accidentally when multiple aliquots are withdrawn from a container which holds multiple doses of a medicament.

**[00150]** A number of preservatives are available which can kill or prevent the growth of commonly encountered contaminants; these contaminants include, but are not limited to the bacteria *P. aeruginosa, E. coli and S. aureus; the yeast C. albicans*; and the mold *A. brasiliensis*. In various embodiments, the preservative comprises benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

**[00151]** The preservative or preservatives are present in an amount which is effective to impart the desired preservative characteristics and allows the final composition to comply with the European Pharmacopoeia 2011 Test for Efficacy of Antimicrobial Preservation, satisfying at least the B criteria for parenterals, and the United States Pharmacopeia 2011 Guidelines for Antimicrobial Effectiveness Testing for Category 1 (injectable) products.

Method of Preparing the Injectable Compositions

**[00152]** The stable injectable compositions of the present application can be made by mixing from about 900 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese with water to form 1 mL of the injectable composition. I

**[00153]** The components of the trace elements can be mixed in any order. For example, one or more trace

elements can be added together and then mixed with water to form a solution having the desired concentration. The mixed trace elements solution pH can be adjusted to a desired value and then the pH adjusted solution can, optionally, be filtered through one or more 0.22 µm sterile filters. The filtered solution can then be filled into the desired container to form the injectable trace elements solution suitable for addition to a parenteral nutrition.

**[00154]** In some embodiments, the injectable compositions of one or more trace elements comprises, consists essentially of, or consists of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition. These trace element compositions are useful for applications to adult and/or pediatric patients.

**[00155]** A pediatric patient includes a patient known to be less than 15 years of age. In some embodiments, the pediatric patient has a weight of less than 36 kg, but greater than 10 kg of body weight.

**[00156]** In other embodiments, the stable injectable composition of one or more trace elements comprises, consists essentially of, or consists of 1000 µg of zinc, 60 µg of copper, 6 µg of selenium, and 3 µg of manganese per 1 mL of the injectable composition. These trace element injectable compositions are useful for applications to neonates.

**[00157]** A neonate includes an infant aged 1 month or younger. In some embodiments, the neonate is less than 10 kg of body weight.

**[00158]** In some embodiments, the new trace element compositions of the current application have reduced amounts of zinc, copper, manganese and no detectable chromium compared to the Multitrace®-5 concentrated, while the selenium amount is the same. For example, the amount of selenium for the adult Multitrace®-5 concentrated composition and the new adult/pediatric composition is the same, which is 60 mcg/mL selenium. The other trace elements in the new adult/pediatric composition of the current application are zinc, copper, and manganese, which are in reduced amounts --mainly 3000 mcg/mL zinc, 300 mcg/mL copper, 55 mcg/mL manganese, and no detectable chromium compared to the Multitrace®-5 concentrated composition as shown in Table 35.

**[00159]** In some embodiments, for the new neonatal composition, compared to the Multitrace®-4 neonatal composition, the zinc, copper, and manganese are in reduced amounts --mainly 1000 mcg/mL zinc, 60 mcg/mL copper, 3 mcg/mL manganese compared to the Multitrace®-4 neonatal composition. However, the selenium for the new neonatal composition is 6 mcg/mL, which is increased as shown in Table 35.

**[00160]** In some embodiments, both the new adult/pediatric composition and the new neonatal composition have no detectable chromium, which is unlike other commercially available compositions (e.g., ADDAMEL™, Multitrace®-5, and Multitrace®-4) as shown in Table 35.

**[00161]** In many aspects, the trace elements of the injectable composition are elemental metals, for example, the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection. In other aspects, the trace elements are sourced from salts of these metals. For example, the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and the elemental selenium is from selenious acid. In these compositions, at least one of the zinc comprises from about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises from about 0.05 wt. percent to about 0.13 wt. percent, the manganese comprises from about 0.026 wt. percent to about 0.013 wt. percent, the selenium comprises from about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 98.5 of the injectable composition based on a total weight of the injectable composition.

**[00162]** In many cases, in the trace elements injectable composition prepared by the above method, the zinc is sourced from zinc sulfate heptahydrate at a dose of from about 2.5 to about 7 mg/day, the copper is sourced form cupric sulfate pentahydrate at a dose of from about 0.5 to about 1.5 mg/day, the manganese is sourced from manganese sulfate monohydrate at a dose of from about 0.15 to about 0.8 mg/day, and the selenium is sourced from selenious acid at a dose of from about 20 to about 60 µg/day. In some other embodiments, the method of preparing the trace elements composition of this disclosure provides an injectable composition where the zinc is zinc sulfate heptahydrate at a dose of from about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of from about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of from about 0.015 to about 0.08 mg/day, and the selenium is sourced selenious acid at a dose of from about 20 to about 60 µg/day. In some embodiments, selenious acid, is a weak acid and it can form salts with metal oxides and hydroxides, such as potassium, zinc, copper, manganese, calcium, or molybdenum. It can also form salts with ammonia (e.g., ammonium selenite) and organic bases.

**[00163]** In many instances the pH of the trace elements composition varies in a range from about 1.0 to about 9. In some instances, the pH of the trace elements composition can be about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9 to about 9.0.

**[00164]** In some embodiments, the pH of the trace elements composition can be adjusted using pH adjusting

agents including organic or inorganic acids and bases. Suitable acids include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid or the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid or the like. Suitable inorganic bases include, but are not limited to, sodium hydroxide, potassium hydroxide, K2CO3, Na2CO3, K3PO4, Na3PO4, K2HPO4, Na2HPO4, organic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, ethanolamine, 2-diethylaminoethanol, lysine, arginine, histidine or the like.

**[00165]** In various embodiments, gamma radiation is used in the terminal sterilization step, which involves utilizing ionizing energy from gamma rays that penetrate deeply into a vial containing the injectable composition of this disclosure. Gamma rays are highly effective in killing microorganisms, they leave no residues, nor do they have sufficient energy to impart radioactivity to the apparatus. Gamma rays can be employed when the injectable composition is a vial or ampule because gamma ray sterilization does not require high pressures or vacuum conditions, and thus the container of the injectable composition is not stressed.

**[00166]** In other embodiments, electron beam (e-beam) radiation may be used to sterilize the injectable composition described in this disclosure. E-beam radiation comprises a form of ionizing energy, which is generally characterized by low penetration and high-dose rates. E-beam irradiation is similar to gamma ray processing in that it alters various chemical and molecular bonds on contact, including the reproductive cells of microorganisms. Beams produced for e-beam sterilization are concentrated, highly charged streams of electrons generated by the acceleration and conversion of electricity.

**[00167]** Autoclaving is usually performed in an autoclave. An autoclave uses pressurized steam as their sterilization agent. The basic concept of an autoclave is to have each item sterilized -whether it is a liquid, plastic ware, or glassware- come in direct contact with steam at a specific temperature and pressure for a specific amount of time. Time, steam, temperature, and pressure are the four main parameters required for a successful sterilization using an autoclave.

**[00168]** The amount of time and temperature required for sterilization of a vial or ampule containing the injectable composition can use higher temperatures for sterilization and requires shorter times. The most common temperatures used are 121 ºC and 132 ºC. In order for steam to reach these high

temperatures, steam has to be pumped into the chamber at a pressure higher than normal atmospheric pressure. In various embodiments, a terminal sterilization feasibility study confirmed that the finished product is stable and can maintain its characteristics upon terminal sterilization. Thus, in various embodiments, the trace elements injectable compositions of this application are terminally sterilized at 122.2ºC for 15 minutes.

**[00169]** The injectable compositions of the present disclosure are packaged in pharmaceutically acceptable containers. Pharmaceutically acceptable containers include intravenous bags, bottles, vials, and/or syringes. In certain embodiments, the containers include intravenous bags and syringes, which can be polymer-based, and vials and intravenous bottles, which can be made of glass. In some embodiments, the components of the container that come into contact with the pharmaceutical composition do not contain polyvinylchloride (PVC). In various aspects, the container is an intravenous bag that does not have any PVC containing components in contact with the pharmaceutical composition. It is also desirable to protect the pharmaceutical compositions from light. Therefore, the container may, optionally, further comprise a light barrier. In certain embodiments, the light barrier can be an aluminum over a pouch.

**[00170]** In many aspects, the present disclosure also provides methods for preparing sterile pharmaceutical compositions. Examples of suitable procedures for producing sterile pharmaceutical drug products include, but are not limited to, terminal moist heat sterilization, ethylene oxide, radiation (i.e., gamma and electron beam), and aseptic processing techniques. Any one of these sterilization procedures can be used to produce the sterile pharmaceutical compositions described herein.

**[00171]** Sterile pharmaceutical compositions may also be prepared using aseptic processing techniques. Sterility is maintained by using sterile materials and a controlled working environment. All containers and apparatus are sterilized, preferably by heat sterilization, prior to filling. Then, the container is filled under aseptic conditions, such as by passing the composition through a filter and filling the units. Therefore, the compositions can be sterile filled into a container to avoid the heat stress of terminal sterilization.

Method of Preparing Parenteral Nutrition

**[00172]** The trace elements of the current application include lower daily amounts of at least one of zinc, copper, chromium and/or manganese per 1mL of the composition than currently available products.

**[00173]** In some embodiments, the trace elements composition contains little or no chromium. The chromium that is present can be present as an impurity and not to exceed about 1 µg and, in other aspects, not to exceed 0.5 µg, in other embodiments, not to exceed about 0.25 µg/mL, and in other embodiments, not to exceed 0.1 µg/mL. In other instances, the injectable composition contains from about 0.0001 µg/mL to about 0.25 µg/mL of chromium. Therefore, when the trace element is added to the PN (e.g., PN of one liter or more), the PN will have no added chromium but may, in some embodiments, contain a chromium impurity from about 0.0001 µg/mL to about 0.25 µg/mL, or in some embodiments, no chromium.

**[00174]** In some embodiments, the amount of chromium in the parenteral nutrition containing the trace elements composition or the trace elements composition itself is not more than about 0.15 µg/mL to not more than about 0.07 µg/mL or lower. With the not more than about 0.15 µg/mL of chromium, the maximum potential exposure to chromium (e.g., 0.045 µg/kg/day) will be 22.5% of the maximum chromium dose that can be used for parenteral nutrition in a target patient population ( e.g., children (weighing 0.4 – 9.9 kg)). This can be based on a target dose volume of, for example, 0.3 mL/kg/day. In some embodiments, this will reduce the risk of toxicity from total chromium exposure in the parenteral nutrition (e.g., from intentionally added chromium and chromium as an impurity).

**[00175]** The trace elements in solution form can be added to the parenteral nutrition typically at a port of the parenteral nutrition container using aseptic technique and, optionally, under a laminar flow hood. The parenteral nutrition can have essential and non-essential amino acids, dextrose, water, lipids, and/or electrolytes in it.

**[00176]** In many embodiments, a method of making a parenteral nutrition containing trace elements is provided. The method comprises adding trace elements to the parenteral nutrition, the trace elements comprising about 900 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 250 mL to about 4000 mL of the parenteral nutrition, the parenteral nutrition comprising at least one of amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof. In some cases, the parenteral nutrition obtained by this method contains 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 250 mL to about 4000 mL of the parenteral nutrition. In other cases, the parenteral nutrition obtained by this method contains 1000 µg of zinc, 60 µg of copper, 6 µg of selenium, and 3 µg of manganese per 1 mL of the injectable composition per 250 mL to about 4000 mL of the parenteral nutrition.

**[00177]** In yet other cases, in the parenteral nutrition the zinc comprises zinc sulfate or zinc sulfate

heptahydrate in an amount of about 13.1 mg to about 13.3 mg, the copper comprises cupric sulfate or cupric sulfate pentahydrate in an amount of about 1.1 mg to about 1.2 mg, the manganese comprises manganese sulfate or manganese sulfate monohydrate in an amount of about 0.16 mg to about 0.18 mg and the selenium comprises selenious acid in an amount of about 95 µg to about 99 µg per about 250 mL to 4000 mL of parenteral nutrition. In another embodiment, the parenteral nutrition obtained by this method comprises zinc sulfate or zinc sulfate heptahydrate in an amount of about 13.2 mg, cupric sulfate or cupric sulfate pentahydrate of the parenteral nutrition in an amount of from about 1.179 mg, manganese sulfate or manganese sulfate monohydrate in an amount of about 0.0169 mg and the selenious acid is in an amount of about 98 µg per 250 mL to 4000 mL of parenteral nutrition.

**[00178]** In some embodiment, there is a method of making a parenteral nutrition containing trace elements at least one of (i) the amino acid comprises lysine hydrochloride, phenylalanine, leucine, valine, threonine, methionine, isoleucine, tryptophan, alanine, arginine, glycine, proline, histidine, glutamic acid, serine, aspartic acid, tyrosine or a mixture thereof; (ii) the dextrose comprises dextrose monohydrate; (iii) the lipid comprises soybean oil, phospholipid, glycerin or a mixture thereof; or (iv) the electrolyte comprises sodium acetate trihydrate, potassium chloride, sodium chloride, potassium acetate, sodium glycerophosphate anhydrous, magnesium sulfate heptahydrate, calcium chloride dihydrate, calcium gluconate or a mixture thereof. In the parenteral nutrition provided by this method, the dextrose comprises dextrose 5%, dextrose 10%, dextrose 20 %, dextrose 25%, or dextrose 50% in water.

**[00179]** The parenteral nutrition provided by this method is stable when stored from about 2 ºC to about 8 ºC for up to about 14 days. In many instances, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition maintained a pH from about 5.50 to about 5.90 and, in some cases, a pH from about 4.5 to about 7.

**[00180]** In some embodiments, the 14 days stability is measured from the time when the trace elements composition is added at room temperature to the parenteral nutrition. In some embodiments, the 14 days stability is measured from the time when the trace elements composition is added at room temperature to the parenteral nutrition and then stored under refrigeration at 2 ºC to about 8 ºC. In some embodiments, the 14 days stability is measured from the time when the trace elements composition is added at room temperature to the parenteral nutrition and about to be administered to the patient, but is not and then is stored under refrigeration at 2 ºC to about 8 ºC for the 14 days.

**[00181]** Further, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition

comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm. In other cases, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition did not exhibit microbial growth when in contact with bacteria such as *S. aureus, P. aeruginosa, E. coli, C. albicans, A. brasiliensis* or a mixture thereof.

Method of Use of the Injectable Compositions

**[00182]** After addition of the trace elements to the parenteral nutrition, the parenteral nutrition can then be connected to an IV tube set and the parenteral nutrition administered via infusion over the desired period of time to the patient (e.g., 24 hours).

**[00183]** The parenteral nutrition can be used to provide a source of calories, protein, electrolytes, or essential fatty acids for adult patients requiring parenteral nutrition. In some embodiments, the method of the present application includes administering to a patient in need thereof an injectable parenteral nutrition formulation comprising at least one of amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof. Therefore, one or more trace elements (e.g., zinc, copper, selenium, manganese) can be added to injectable amino acids, dextrose, water, lipids, electrolytes, or a combination thereof based on the specific need of the patient.

**[00184]** The trace elements can be a single trace element (e.g., zinc alone) or a combination of trace elements (e.g., zinc, copper, selenium, manganese) that can be added to the injectable amino acids, dextrose, water, lipids, electrolytes or a combination thereof based on the specific need of the patient.

**[00185]** In various other embodiments, the parenteral nutrition comprises from about 900 µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 250 mL to 4000 mL of the parenteral nutrition. In some aspects, the parenteral nutrition comprises, consists essentially of, or consists of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 250 mL to about 4000 mL of the parenteral nutrition. In some aspects, the parenteral nutrition comprises, consists essentially of, or consists of 1,000 µg of zinc, 60 µg of copper, 6 µg of selenium, and 3 µg of manganese per 250 mL to about 4000 mL of the parenteral nutrition.

**[00186]** In other aspects, the zinc comprises zinc sulfate or zinc sulfate heptahydrate in an amount of about 13.1 mg to about 13.3 mg, the copper comprises cupric sulfate or cupric sulfate pentahydrate in an amount of about 1.1 mg to about 1.2 mg, the manganese comprises manganese sulfate or manganese sulfate monohydrate in an amount of about 0.16 mg to about 0.18 mg and the selenium

comprises selenious acid in an amount of about 95 µg to about 99 µg per about 250 mL to 4000 mL of parenteral nutrition. In yet other aspects, the zinc sulfate or zinc sulfate heptahydrate is in an amount of about 13.2 mg, the cupric sulfate or the cupric sulfate pentahydrate is in an amount of about 1.179 mg, the manganese sulfate or manganese sulfate monohydrate is in an amount of about 0.169 mg and the selenious acid is in an amount of about 98 µg.

**[00187]** In many embodiments, the at least one of the amino acid useful in the method of providing a source of calories comprises lysine hydrochloride, phenylalanine, leucine, valine, threonine, methionine, isoleucine, tryptophan, alanine, arginine, glycine, proline, histidine, glutamic acid, serine, aspartic acid, tyrosine or a mixture thereof. The dextrose useful in this method includes dextrose monohydrate, anhydrous and hydrous forms of dextrose, for example, dextrose 5%, dextrose 10%, dextrose 20 %, dextrose 25%, or dextrose 50% in water. or a combination thereof. Useful lipids include without limitation soybean oil, phospholipid, glycerin, or a mixture thereof. The electrolyte can comprise sodium acetate trihydrate, potassium chloride, sodium chloride, potassium acetate, sodium glycerophosphate anhydrous, magnesium sulfate heptahydrate, calcium chloride dihydrate, calcium gluconate or a mixture thereof.

**[00188]** In various aspects, the parenteral nutrition used in the method of providing a source of calories, protein, electrolytes, or essential fatty acids is nonpyrogenic and can have a pH that can vary from about 3.5 to about 7.9.

**[00189]** It has been surprisingly found that the parenteral nutrition used in the method of providing a source of calories, protein, electrolytes, or essential fatty acids is stable when stored from about 2 ºC to about 8 ºC for up to about 14 days. In many aspects, the stable parenteral nutrition when stored from about 2 ºC to about 8 ºC for about 14 days can maintain a pH from about 5.50, 5.60, 5.70, 5.80 to about 5.90. In various instances, when stored from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm. Also, when stored at from about 2 ºC to about 8 ºC for about 14 days, the parenteral nutrition did not exhibit microbial growth caused by such microbes as, for example, *S. aureus, P. aeruginosa, E. coli, C. albicans, A. brasiliensis* or a mixture thereof.

**[00190]** In various embodiments, a method of maintaining plasma trace elements in a patient in need thereof is provided. The method of maintaining plasma trace elements comprises administering at least an injectable composition to the patient, the injectable composition comprising water, from about 900

µg to about 4,000 µg of zinc, from about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, and from about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition. In many aspects, when the injectable composition is stored from about 2 ºC to about 8 ºC for about 14 days, then the injectable composition comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm. In other aspects, when stored from about 2 ºC to about 8 ºC for about 14 days, the injectable composition did not exhibit microbial growth caused by any one of several microbes, for example, S. aureus, P. aeruginosa, E. coli, C. albicans, A. brasiliensis or a mixture thereof. In many cases, when stored from about 2 ºC to about 8 ºC for about 14 days, the injectable composition maintained a pH from about 5.50 to about 5.90.

**[00191]** In various embodiments, the method of maintaining plasma trace elements in a patient in need thereof further comprises treating patients having a negative nitrogen balance. In other embodiments, the method of maintaining plasma trace elements in a patient in need thereof further comprises the use of the electrolyte as a supplement to intravenous solutions given for parenteral nutrition to maintain plasma levels of anyone of zinc, copper, manganese or selenium or a mixture thereof to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

**[00192]** These and other aspects of the present application will be further appreciated upon consideration of the following examples, which are intended to illustrate certain particular embodiments of the application, but they are not intended to limit its scope, as defined by the claims.

EXAMPLES

**[00193]** Examples of the stable, ready-to-use injectable compositions containing trace elements such as zinc, copper, selenium, and manganese are described in some of the examples below. The examples also include parenteral nutrition solutions with or without the stable injectable compositions having trace elements such as zinc, copper, selenium, and manganese. The trace elements of the current application include lower daily amounts of at least one of zinc, copper, chromium, and/or manganese per 1mL of the trace element solution than currently available products. When added to parenteral solution the parenteral solution containing the trace elements remained stable for about at least 3 days up to 14 days under refrigeration.

**[00194]** Example 1

**[00195]** In this example, an injectable sterile, nonpyrogenic solution including trace elements of

zinc, copper, manganese, and selenium is prepared by mixing these elements with water for injection to form 1 mL of injectable composition per single dose vial. This composition contains not more than 1.0 µg chromium in conformance with USP formulation requirements. The formulation is summarized in Table 6.

**[00196]** Table 6 – Injectable Composition

| Ingredient Name | Quantity per mL | Elemental Equivalent |
|---|---|---|
| Zinc Sulfate•7$H_2O$, USP | 13.20 mg | 3 mg Zn/mL |
| Cupric Sulfate•5$H_2O$, USP | 1.18 mg | 0.3 mg Cu/mL |
| Manganese Sulfate•$H_2O$, USP | 169.00 mcg | 55 µg Mn/mL |
| Selenious Acid, USP | 98.00 mcg | 60 µg Se/mL |
| Sulfuric Acid, NF | N/A | N/A |
| Water for Injection, USP | Q.S. to 1 mL | N/A |

N/A = Not Applicable

**[00197]** Each mL contains: zinc sulfate, USP (heptahydrate) 13.20 mg (equivalent to 3 mg zinc); cupric sulfate, USP (pentahydrate) 1.18 mg (equivalent to 0.3 mg copper); selenious acid, USP 98 µg (equivalent to 60 µg selenium); manganese sulfate, USP (monohydrate) 169 µg (equivalent to 55 µg manganese); and water for injection, USP q.s. The pH range of the solution is 1.5 to 3.5 and may be adjusted with sulfuric acid, NF.

**[00198]** Example 2

**[00199]** This example discusses studies of known parenteral nutrition admixed with the injectable compositions of trace elements described in this application. Studies of parenteral nutrition (PN) solutions admixed with the injectable compositions of trace elements of this application were conducted over a 3 day and 14-day interval. PN solutions used in these studies were CLINIMIX® and KABIVEN® as listed in Table 7 below.

**[00200]** Table 7 – Parenteral Nutrition

| Type | Ingredient | CLINIMIX E 4.25/25 | CLINIMIX E 4.25/10 | KABIVEN® |
|---|---|---|---|---|
| | Soybean Oil (g/100mL) | --- | --- | 3.9 |
| | Dextrose Hydrous, USP (g/100mL) | 25 | 10 | 9.8 |
| | Amino Acids (g/100mL) | 4.25 | 4.25 | 3.31 |
| | Total Nitrogen (mg/100 mL) | 702 | 702 | 526 |
| Essential Amino Acids | Leucine | 311 | 311 | 263 |
| | Isoleucine | 255 | 255 | 164 |
| | Leucine | --- | --- | 231 |

| | | | | |
|---|---|---|---|---|
| | Valine | 247 | 247 | 213 |
| | Lysine (as the hydrochloride) | 247 | 247 | 263 |
| | Phenylalanine | 238 | 238 | 231 |
| | Histidine | 204 | 204 | 199 |
| | Threonine | 179 | 179 | 164 |
| | Methionine | 170 | 170 | 164 |
| | Tryptophan | 77 | 77 | 55 |
| Nonessential Amino Acids (mg/100 mL) | Alanine | 880 | 880 | 467 |
| | Arginine | 489 | 489 | 330 |
| | Glycine | 438 | 438 | 231 |
| | Proline | 289 | 289 | 199 |
| | Serine | 213 | 213 | 131 |
| | Aspartic Acid, USP | --- | --- | 99 |
| | Tyrosine | 17 | 17 | 6.7 |
| Electrolytes (mg/100 ml) | Sodium Acetate Trihydrate, USP | 297 | 297 | 239 |
| | Potassium Chloride | ---- | --- | 174 |
| | Sodium Glycerophosphate, Anhydrous | ---- | --- | 147 |
| | Dibasic Potassium Phosphate, USP | 261 | 261 | --- |
| | Sodium Chloride, USP | 77 | 77 | --- |
| | Magnesium chloride, USP | 51 | 51 | --- |
| | Magnesium Sulfate Heptahydrate, USP | --- | --- | 96 |
| | Calcium Chloride Dihydrate, USP | 33 | 33 | 29 |
| Electrolyte Profile (mEq/L) | Sodium | 35 | 35 | 31 |
| | Potassium | 30 | 30 | 23 |
| | Magnesium | 5 | 5 | 7.8 |
| | Calcium | 4.5 (2.2 mmol/L) | 4.5 (2.2 mmol/L) | 3.8 (1.9 mmol/L) |
| | Acetate | 70 | 70 | 38 |
| | Chloride | 39 | 39 | 45 |
| | Sulfate | --- | --- | 7.8 |
| | Phosphate (as $HP0_4$) | 30 (15mmol/L) | 30 (15mmol/L) | N.A. (9.7 mmol/L) |
| | pH range | 6.0 (4.5 to 7.0) | 6.0 (4.5 to 7.0) | 5.6 |
| | Osmolarity (mOsmol/L) (calc.) | 1825 | 1070 | 1060 |
| | From Dextrose | 850 | 340 | 330 |
| | From Lipid | ---- | --- | 390 |
| | From Amino Acids | 170 | 170 | 130 |
| | Total (Dextrose, Lipid and Amino Acids) | 1020 | 510 | 1060 |

**[00201]** CLINIMIX E 4.25/25 contained 24% dextrose concentration and was used in a three (3)-

day study. Because this formulation was discontinued, CLINIMIX E 4.25/10 which contained 10% dextrose concentration was used in the 14-day study. The same KABIVEN® formulation described in Table 2 was used in both 3-day and 14-day studies.

**[00202]** In these studies, 1 mL of the injectable trace element composition was added to two (2) L IV PN infusion bags of KABIVEN® and CLINIMIX E. KABIVEN® admixtures with and without 1 mL of Injectable trace element composition were stored for about at least 3 days (72 hours) at 2-8°C. Upon testing as described below the KABIVEN® admixtures met the acceptance criteria of a "no growth" protocol. CLINIMIX E admixtures with and without the introduction of Injectable trace element composition found the admixtures stored for about at least 3 days (72 hours) at either 2°C to 8°C or 20°C to 25°C met the acceptance criteria of "no growth" protocol. Based on the results of these admixture studies, we concluded that the admixture of injectable trace element composition in 2 L infusion PN solutions of KABIVEN® and CLINIMIX E supported the manufacturers' original package insert labeling recommendations for KABIVEN® and CLINIMIX E.

**[00203]** For example, for KABIVEN®, the labeling recommendation states that "KABIVEN® should be used immediately after mixing and the introduction of additives. If not used immediately, the storage time and conditions prior to use should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage at 2° to 8°C (36° to 46°F), the admixture should be infused within 24 hours. Any mixture remaining must be discarded."

**[00204]** For CLINIMIX E the labeling recommendations caution "Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a period, no longer than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any mixture remaining must be discarded."

**[00205]** In order to establish stability data for parenteral nutrition admixed with the injectable compositions of trace elements, we conducted a stability study of injectable trace element composition (trace elements injectable composition, USP) in parenteral nutrition admixtures (assay test); a pH study of parenteral nutrition (PN) admixtures upon addition of injectable trace element composition (trace elements injectable composition, USP); a compatibility study of injectable trace element composition (trace elements injectable composition, USP) in parenteral nutrition admixtures; and a reduced inoculation antimicrobial effectiveness study for injectable trace element composition (trace elements injectable composition, USP) in parenteral nutrition admixtures.

**[00206]** These studies were intended to support the USP <797> medium risk storage for up to 9 days

under refrigeration [2° to 8°C (36° to 46°F)]. At the time of initiating the 14-day admixture studies, it was noted that the current package insert (PI) labeling of KABIVEN® and CLINIMIX now includes the following beyond use dating (BUD) statements for storage:

**[00207]** For KABIVEN®: In the absence of additives, once activated, KABIVEN® remains stable for 48 hours at 25°C (77° F). If not used immediately, the activated bag can be stored for up to 7 days under refrigeration [2° to 8°C (36° to 46°F)]. After removal from refrigeration, the activated bag should be used within 48 hours. For CLINIMIX E: Storage after removal of overwrap: once removed from the protective clear overwrap, mixed (peel seal activated) or unmixed (peel seal intact), CLINIMIX E solutions may be stored under refrigeration for up to 9 days. The results or our studies are discussed in examples 3, below.

**[00208]** Example 3 - Stability Study of Injectable trace element composition (Trace elements injectable composition, USP) in Parenteral Nutrition Admixtures Assay Test

**[00209]** In this example, we evaluated whether the addition of an injectable trace element composition to parenteral nutrition (PN) admixtures would result in chemical degradation of individual ingredients under the prescribed in-use condition of up to 14 days. The PN admixtures were assay tested for zinc, copper, selenium, and manganese. Chromium was evaluated as a potential elemental impurity.

**[00210]** In this example, control PN admixtures (e.g., without an injectable trace element composition) of KABIVEN® and CLINIMIX E were tested for trace element levels of zinc, copper, selenium, manganese, and chromium and the findings are summarized in Tables 8 and 10 below. Tables 9 and 11 illustrate assay results of a KABIVEN® and CLINIMIX E PN IV solutions treated with the injectable trace element composition of this application and stored 14 days at 2°C to 8°C.

**[00211]** Table 8 – Assay Results for KABIVEN® Control Admixtures without Injectable Trace Element Composition

| Assay | Zinc | Copper | Selenium | Manganese | Chromium |
|---|---|---|---|---|---|
| Results | < 750 µg/L | < 75 µg/L | < 15 µg/L < | < 13.7 µg/L | < 0.25 µg/mL |

**[00212]** Table 9 - Assay Results for Injectable Trace Element Composition in KABIVEN® Solution Stored 14 days at 2°C to 8°C

| Assay | Acceptance Criteria | Day 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Zinc | 90.0 – 110.0 % | 96.5 | 93.9 | 93.8 | 97.0 | 96.0 |
| Copper | 90.0 – 110.0 % | 101.8 | 98.7 | 97.8 | 99.9 | 105.5 |
| Selenium | 90.0 – 110.0 % | 92.6 | 93.5 | 97.9 | 92.6 | 90.8 |
| Manganese | 90.0 – 110.0 % | 100.7 | 95.0 | 92.1 | 102.5 | 97.9 |

**[00213]** Table 10 – Assay Results for CLINIMIX E Control PN Admixture without Injectable Trace Element Composition

| Assay | Zinc | Copper | Selenium | Manganese | Chromium |
|---|---|---|---|---|---|
| Results | < 750 µg/L | < 75 µg/L | < 15 µg/L | < 13.7 µg/L | < 0.25 µg/mL |

**[00214]** Table 11 - Assay Results for Injectable trace element composition in CLINIMIX Solution Stored for 14 days at 2°C to 8°C

| Assay | Acceptance Criteria | Day 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| Zinc | 90.0 – 110.0 % | 98.5 | 94.4 | 96.5 | 96.2 | 96.3 |
| Copper | 90.0 – 110.0 % | 109.7 | 98.8 | 101.5 | 101.0 | 106.0 |
| Selenium | 90.0 – 110.0 % | 108.8 | 102.0 | 104.2 | 101.2 | 95.7 |
| Manganese | 90.0 – 110.0 % | 105.0 | 97.2 | 98.9 | 101.6 | 106.8 |

**[00215]** The results of this study show that assay values of parenteral nutrition solutions of KABIVEN® and CLINIMIX E in two (2) L infusion solutions each spiked with 1.0 mL of injectable trace element composition and stored under refrigeration (2°C to 8°C) remained within the protocol acceptance criteria of 90.0 – 110.0 % acceptance criteria for the fourteen (14) day duration of the study.

**[00216]** Example 4 - pH Study of Parenteral Nutrition (PN) Admixtures upon Addition of Injectable trace element composition (Trace elements injectable composition)

**[00217]** In this example, a study was conducted to evaluate pH changes before and after the addition of injectable trace element composition added to PN solutions of KABIVEN® and CLINIMIX E. The study was conducted to determine if the addition of the injectable trace element composition of this disclosure would significantly change the pH of the PN admixtures under the prescribed in-use

conditions. The pH measurements were performed at Day 0, Day 5, Day 7, Day 10 and Day 14 on samples stored at 2°C to 8°C and the results are illustrated in Tables 12 and 13. In the assays summarized in Tables 9 and 10, the control sample is either KABIVEN® or CLINIMIX E PN mixture as found in an IV bag or TE-4 represents a bag of KABIVEN® or CLINIMIX E to which 1.0 mL of injectable trace element composition containing zinc, copper, selenium, and manganese was added.

**[00218]** Table 12 - pH Results for Injectable Trace Element Composition added to KABIVEN® Solution Stored 14 days at 2°C to 8°C

| Test | Acceptance Criteria | Day 0 | | Day 5 | | Day 7 | | Day 10 | | Day 14 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 |
| pH | Record results | 5.52 | 5.51 | 5.51 | 5.51 | 5.49 | 5.50 | 5.50 | 5.49 | 5.50 | 5.50 |

**Control =** bag of KABIVEN®

**TE-4 =** bag of KABIVEN® with added 1.0 mL of injectable trace element composition including Zn, Cu, Mn, and Se.

**[00219]** Table 13 - pH Results for Injectable trace element composition added to CLINIMIX Solution Stored 14 days at 2°C to 8°C

| Test | Acceptance Criteria | Day 0 | | Day 5 | | Day 7 | | Day 10 | | Day 14 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 |
| pH | Record results | 5.86 | 5.87 | 5.85 | 5.85 | 5.86 | 5.85 | 5.86 | 5.86 | 5.87 | 5.86 |

**Control =** bag of CLINIMIX

**TE-4 =** bag of CLINIMIX with added 1.0 mL of Injectable trace element composition including Zn, Cu, Mn, and Se.

**[00220]** The results of these studies illustrate that pH of KABIVEN® and CLINIMIX E PN solutions, each spiked with 1.0 mL of Injectable trace element composition did not differ from the pH of their respective control samples. In addition, the pH of KABIVEN® control, CLINIMIX E and samples spiked with injectable trace element composition was unchanged after storage under refrigeration from 2 °C to 8 °C for up to 14 days.

**[00221]** Based on the results of these studies, it can be concluded that the addition of 1.0 mL of injectable trace element composition to the 2 L solution of KABIVEN® and/or CLINIMIX E will not

alter the pH of the PN solutions when stored for 14 days at refrigeration (2 °C to 8 °C).

**[00222]** Example 5 - Compatibility Study of Injectable trace element composition (Trace elements injectable composition, USP) in Parenteral Nutrition Admixtures

**[00223]** The studies summarized in Tables 14, 15, 16 and 17 were initiated to assure that the injectable trace element composition of this disclosure and PN solutions of KABIVEN and CLINIMIX E are physically compatible. The PN admixtures with and without the injectable trace element composition were tested for visual examination and particulate matter (PM) by means of USP <788> Method 2 (Microscopic Particle Count Test). The testing was performed at Day 0, Day 5, Day 7, Day 10, and Day 14 on samples stored at 2-8°C.

**[00224]** Table 14- PM Results for Injectable trace element composition (TE-4) in KABIVEN® Bags Stored 14 days at 2°C to 8°C

| Test | Acceptance Criteria | 0 days | | 5 days | | 7 Days | | 10 days | | 14 Days | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 |
| Visual Examination | Precipitates have not formed during the addition of Injectable trace element composition | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms |
| | The emulsion has not separated. | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms |
| Particulate Matter <788>: Method 2 Microscopic | NMT 12 particles per 1 mL that are ≥ 10 µm. | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 |
| | NMT 2 particles per 1 mL that are ≥ 25 µm. | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Particle Count Test | 100 µm (for informational purposes only) | 0 | 0 | 0 | 0 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 |

Control = bag of KABIVEN®

TE-4 = bag of KABIVEN® with added 1.0 mL of injectable trace element composition including Zn, Cu, Mn, and Se.

**[00225]** Table 15 Particle Categorization for Injectable trace element composition in KABIVEN® Bags Stored 14 days at 2°C to 8°C

| Test Station | Particle Description | |
|---|---|---|
| | Control | TE-4 |
| 0 Days | Major: dark particles (10-50µm)<br>Minor: light particles (10-40µm), polymeric (20-70µm)<br>≥100µm: no particles noted | Major: dark particles (10-40µm)<br>Minor: light particle (10-40µm), polymeric (20- 70µm)<br>≥100µm: no particles noted |
| 5 Days | Major: light particles (10-80µm)<br>Minor: dark particles (10-70µm), polymeric (30-80µm)<br>≥100µm: no particles noted | Major: dark particles (10-70µm)<br>Minor: light particles (10-70µm), polymeric (60µm)<br>≥100µm: no particles noted |
| 7 Days | Major: dark particles (10-40µm)<br>Minor: light particles (10-30µm), polymeric (30-<br>>100µm), fibrous (80µm)<br>≥100µm: polymeric (190µm, 240µm) | Major: dark particles (10-60µm)<br>Minor: light particles (10-40µm), polymeric (30- 50µm)<br>≥100µm: fibrous (310µm) |
| 10 days | Major: dark particles (10-40µm)<br>Minor: light particles (10-60µm), polymeric (20-<br>>100µm)<br>≥100µm: fibrous (180µm), polymeric (270µm) | Major: dark particles (10-40µm)<br>Minor: light particles (10-50µm), polymeric (20-<br>>100µm)<br>≥100µm: polymeric (200µm) |
| 14 Days | Major: dark particles (10-80µm)<br>Minor: light particles (10-40µm), polymeric (20- > 100µm)<br>≥100µm:polymeric (290µm, 170µm, 140µm, 210, 250µm, 200µm) | Major: dark particles (10-70µm)<br>Minor: light particles (10-80µm), polymeric (20- 90µm)<br>≥100µm: no particles noted |

Control = bag of KABIVEN®

TE-4 = bag of KABIVEN® with added 1.0 mL of injectable trace element composition including Zn, Cu, Mn, and Se.

**[00226]** Table 16 – Particulate Matter Results for Injectable Trace Element Composition in CLINIMIX E Bags Stored 14 Days at 2°C to 8°C

| Test | Acceptance Criteria | 0 days | | 5 days | | 7 Days | | 10 days | | 14 Days | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | TE-4 | Contro | TE-4 | Control | TE-4 | Control | TE-4 | Control | TE-4 |
| Visual Examination | Precipitates have not formed during the addition of injectable trace element composition | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms |
| | The emulsion has not separated. | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms | NA | Conforms |
| Particulate Matter <788>: Method 2 Microscopic Particle Count Test | NMT 12 particles per 1 mL that are ≥ 10 µm. | < 1 | < 1 | < 1 | < 1 | < 1 | 1 | 1 | 1 | < 1 | < 1 |
| | NMT 2 particles per 1 mL that are ≥ 25 µm. | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 |
| | 100 µm (for informational purposes only) | 0 | < 1 | < 1 | < 1 | 0 | 0 | 0 | < 1 | < 1 | 0 |

Control = bag of CINIMIX E™

TE-4 = bag of CINIMIX E with added 1.0 mL of Injectable trace element composition including Zn, Cu, Mn, and Se.

**[00227]** Table 17 - Particle Categorization for Injectable trace element composition in CLINIMIX E Bags Stored 14 Days at 2°C to 8°C

| Test | Particle Description |
|---|---|

| Station | Control | TE-4 |
|---|---|---|
| 0 Days | Major: dark particles (10-60µm)<br>Minor: light particles (10-70µm), polymeric (80µm), fibrous (90µm)<br>≥100µm: no particles noted | Major: dark particles (10-90µm)<br>Minor: light particle (10-70µm), polymeric (80µm)<br>≥100µm: fibrous (460µm) |
| 5 Days | Major: dark particles (10-50µm)<br>Minor: light particles (10-40µm), polymeric (20- 70µm)<br>≥100µm: fibrous (380µm) | Major: dark particles (10-90µm)<br>Minor: light particles (10-70µm), polymeric (20µm- 60µm)<br>≥100µm: fibrous (150µm, 170µm, 260µm) |
| 7 Days | Major: dark particles (10-80µm)<br>Minor: light particles (10-70µm), polymeric (20- 60µm)<br>≥100µm: no particles noted | Major: dark particles (10-80µm)<br>Minor: light particles (10-90µm), polymeric (20- 90µm)<br>≥100µm: no particles noted |
| 10 days | Major: dark particles (10-80µm)<br>Minor: light particles (10-70µm), polymeric (20- 90µm)<br>≥100µm: no particles noted | Major: dark particles (10- >100µm)<br>Minor: light particles (10-80µm), polymeric (70µm)<br>≥100µm: dark particle (160µm) |
| 14 Days | Major: dark particles (10-50µm)<br>Minor: light particles (10-90µm), polymeric (20- 90µm), fibrous (30->100µm) | Major: dark particles (10-50µm)<br>Minor: light particles (10-80µm), polymeric (20- 80µm)<br>≥100µm: no particles noted |

Control = bag of CINIMIX E
TE-4 = bag of CINIMIX E with added 1.0 mL of Injectable trace element composition including Zn, Cu, Mn, and Se.

**[00228]** The compatibility study results for both, the control and admixture samples illustrated in Tables 14, 15, 16 and 17 indicated that particulate matter in these samples remained within USP <788> limits for large volume parenteral solutions. In addition, the consistency of the particle counts and particle morphologies of the control and injectable trace element composition admixture samples, demonstrated no evidence of incompatibility.

**[00229]** Based on the results of this study, injectable trace element composition containing zinc, copper, selenium, and manganese of this application is compatible with KABIVEN® and CLINIMIX E solutions when stored for 14 days at refrigeration (2°C to 8°C).

**[00230]** Example 6 - Reduced Inoculation Antimicrobial Effectiveness Study for Injectable trace element composition (Trace elements injectable composition, USP) in Parenteral Nutrition Admixtures

**[00231]** In this example, the purpose of the reduced inoculation antimicrobial effectiveness study was to demonstrate whether or not there would be adventitious microbial contamination growth during

the preparation and storage of parenteral nutrition admixtures with injectable trace element composition containing zinc, copper, selenium and manganese. The PN admixtures of Kobiven ® and CLINIMIX E treated with injectable trace element composition were challenged with five appropriate compendial microorganisms (i.e., Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, and Aspergillus brasiliensis) at low inoculum levels 10–100 colony forming units/mL (CFU) for up to 14 days at 2-8°C storage conditions.

**[00232]** It is noted that the inoculum concentration of Candida albicans exceeded protocol upper limit of 100 CFU/mL (obtained 120 CFU/mL) had a reported Log CFU recovery of 2.1. There was no impact on the study as the Log CFU recoveries which were accurately enumerated at each time point of the study.

**[00233]** At each test point, the Log CFU recovery values were measured, were 10 – 100 CFU is equivalent to 1 – 2 Log CFU. The acceptance criteria of the protocol was "no growth" which was defined as not more than 0.5 log increases from the calculated inoculum concentration. The results in tables 18, 19, 20, 21, 22, 23, 24, and 25 are reported as Log CFU/mL of product.

**[00234]** Table 18 - Log Recovery Values for KABIVEN® Admixture Bags with Injectable Trace Element Composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | 1.7 | 1.8 | 1.9 | 1.9 | 1.8 |
| *P. aeruginosa* (9027) | 1.6 | 1.8 | 0.9 | 0.8 | 0.5 | 0.5 |
| *E. coli* (8739) | 2.0 | 2.1 | 1.9 | 1.8 | 1.6 | 1.6 |
| *C. albicans* (10231) | 2.1[a] | 2.1 | 2.0 | 2.0 | 2.0 | 2.0 |
| *A. brasiliensis* (16404) | 1.4 | 1.5 | 1.4 | 1.2 | 1.2 | 1.2 |
| *Negative Product (TSA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |
| *Negative Product (SDA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00235]** Table 19: Log Reduction Values for KABIVEN® Admixture Bags with Injectable Trace Element Composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | -0.1 | 0.0 | +0.1 | +0.1 | 0.0 |
| *P. aeruginosa* (9027) | 1.6 | +0.2 | -0.7 | -0.8 | -1.1 | -1.1 |
| *E. coli* (8739) | 2.0 | +0.1 | -0.1 | -0.2 | -0.4 | -0.4 |
| *C. albicans* (10231) | 2.1[a] | 0.0 | -0.1 | -0.1 | -0.1 | -0.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *A. brasiliensis* (16404) | 1.4 | +0.1 | 0.0 | -0.2 | -0.2 | -0.2 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00236]** Table 20: Log Recovery Values for KABIVEN® Admixture Bags without Injectable trace element composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | 2.0 | 1.8 | 1.9 | 2.0 | 1.8 |
| *P. aeruginosa* (9027) | 1.6 | 1.6 | 0.8 | 0.5 | 0.6 | 0.5 |
| *E. coli* (8739) | 2.0 | 2.1 | 1.9 | 1.9 | 1.9 | 1.6 |
| *C. albicans* (10231) | 2.1[a] | 2.0 | 2.0 | 2.0 | 2.1 | 2.1 |
| *A. brasiliensis* (16404) | 1.4 | 1.5 | 1.1 | 1.3 | 1.3 | 1.3 |
| *Negative Product (TSA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |
| *Negative Product (SDA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00237]** Table 21: Log Reduction Values for KABIVEN® Admixture Bags without Injectable Trace Element Composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | +0.2 | 0.0 | +0.1 | +0.2 | 0.0 |
| *P. aeruginosa* (9027) | 1.6 | 0.0 | -0.8 | -1.1 | -1.0 | -1.1 |
| *E. coli* (8739) | 2.0 | +0.1 | -0.1 | -0.1 | -0.1 | -0.2 |
| *C. albicans* (10231) | 2.1[a] | -0.1 | -0.1 | -0.1 | -0.0 | 0.0 |
| *A. brasiliensis* (16404) | 1.4 | +0.1 | -0.3 | -0.1 | -0.1 | -0.1 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00238]** KABIVEN® (contains dextrose, essential and nonessential amino acids with electrolyte and a 20% lipid emulsion) with and without injectable trace element composition containing zinc, copper, manganese and selenium were stored for up to 14 days at 2°C to 8°C met the protocol's acceptance criteria of "no growth." The marginally higher inoculum concentration of C. albicans did not enhance any microbial proliferation within the product.

**[00239]** Table 22: Log Recovery Values for CLINIMIX E Admixture Bags (contains essential and non-essential amino acids with electrolyte in dextrose with calcium) with Injectable trace element composition (2°C

to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | 1.9 | 1.8 | 1.8 | 1.8 | 1.7 |
| *P. aeruginosa* (9027) | 1.6 | 1.9 | 0.9 | 1.1 | 1.0 | 0.7 |
| *E. coli* (8739) | 2.0 | 2.0 | 1.6 | 1.4 | 1.2 | 1.0 |
| *C. albicans* (10231) | 2.1[a] | 2.0 | 2.0 | 2.0 | 1.9 | 1.9 |
| *A. brasiliensis* (16404) | 1.4 | 1.5 | 1.3 | 1.3 | 1.3 | 1.3 |
| *Negative Product (TSA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |
| *Negative Product (SDA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00240]** Table 23: Log Reduction Values for CLINIMIX E Admixture Bags with Injectable trace element composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | +0.1 | 0.0 | 0.0 | 0.0 | -0.1 |
| *P. aeruginosa* (9027) | 1.6 | +0.3 | -0.7 | -0.5 | -0.6 | -0.9 |
| *E. coli* (8739) | 2.0 | 0.0 | -0.4 | -0.6 | -0.8 | -1.0 |
| *C. albicans* (10231) | 2.1[a] | -0.1 | -0.1 | -0.1 | -0.2 | -0.2 |
| *A. brasiliensis* (16404) | 1.4 | +0.1 | -0.1 | -0.1 | -0.1 | -0.1 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00241]** Table 24: Log Recovery Values for CLINIMIX E Admixture Bags without Injectable Trace Element Composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | 2.1 | 1.9 | 1.8 | 1.8 | 1.7 |
| *P. aeruginosa* (9027) | 1.6 | 1.7 | 1.1 | 0.8 | 0.7 | 0.5 |
| *E. coli* (8739) | 2.0 | 2.0 | 1.6 | 1.5 | 1.3 | 1.0 |
| *C. albicans* (10231) | 2.1[a] | 2.0 | 1.9 | 1.9 | 1.9 | 1.9 |
| *A. brasiliensis* (16404) | 1.4 | 1.5 | 1.2 | 1.2 | 1.3 | 1.3 |
| *Negative Product (TSA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |
| *Negative Product (SDA)* | N/A | < 0.0 | < 0.0 | < 0.0 | < 0.0 | < 0.0 |

a. Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00242]** Table 25: Log Reduction Values for CLINIMIX E Admixture Bags without Injectable Trace Element Composition (2°C to 8°C)

| Organism (ATCC) | Inoculated | Time 0 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|
| *S. aureus* (6538) | 1.8 | +0.3 | -0.1 | 0.0 | 0.0 | -0.1 |
| *P. aeruginosa* (9027) | 1.6 | +0.1 | -0.5 | -0.8 | -0.9 | -1.1 |
| *E. coli* (8739) | 2.0 | 0.0 | -0.4 | -0.5 | -0.7 | -1.0 |
| *C. albicans* (10231) | 2.1[a] | -0.1 | -0.2 | -0.2 | -0.2 | -0.2 |
| *A. brasiliensis* (16404) | 1.4 | +0.1 | -0.2 | -0.2 | -0.1 | -0.1 |

**a.** Inoculum concentration exceeded protocol limit of 100 CFU/mL (obtained 120 CFU/mL). There was no impact on the study.

**[00243]** The Log recovery values results of CLINIMIX E IV admixtures with and without injectable trace element composition containing zinc, copper, selenium and manganese found that admixtures stored for up to 14 days at 2°C to 8°C met the protocol's acceptance criteria of "no growth."

**[00244]** The results of the reduced inoculation AME study, found both KABIVEN® and CLINIMIX E admixtures with and without the introduction of injectable trace element composition and stored for up to 14 days under refrigeration (2°C to 8°C) met the protocol's acceptance criteria of "no growth."

**[00245]** Since the results of the four-admixture studies met our acceptance criteria, we concluded that the addition of injectable trace element composition to either 2 L infusion solution (KABIVEN® and/or CLINIMIX E) supports the manufacturers' current package insert (PI) labeling of both KABIVEN® and CLINIMIX E that the PN admixtures are stable for up to 9 days when kept under refrigeration. As a result, a package insert for the injectable trace element composition of this invention can include the following USP <797> medium-risk BUD statements for package insert for refrigerated storage up to 9 days.

**[00246]** Therefore, the package insert for injectable trace element composition has been revised to include the following storage recommendation: "Use parenteral nutrition solutions containing injectable trace element composition promptly after mixing. Any storage of the admixture should be under refrigeration from 2ºC to 8ºC (36ºF to 46ºF) and limited to a period, no longer than 9 days. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture." This package insert statement, in conjunction with our 14-day admixture studies at 2° to 8°C, now provide healthcare professionals, pharmacists and end-users extensive admixture stability information for selenious acid injection, USP, zinc sulfate injection, USP, and injectable trace element composition containing zinc, copper, manganese and selenium (Trace elements injectable composition, USP) in parenteral nutrition infusion solutions under refrigeration [2° to 8°C (36° to 46°F)].

**[00247]** Example 7 –Process for Preparing Trace Elements Injectable Compositions

**[00248]** Three exhibit batches (lot RD15-013, RD16-001, RD16-007) and bridging batch (lot RD18-007) of the trace elements injectable composition, USP formulation were prepared utilizing the equipment and process parameters summarized in Table 26 below.

**[00249]** Table 26 – Process Parameters for Injectable Composition

| Manufacturing Train and Process Parameters | |
|---|---|
| Concentration | Zinc: 3 mg/mL<br>Copper: 0.3 mg/mL<br>Selenium: 60 µg/mL<br>Manganese: 55 µg/mL |
| Batch Size | 60 Liters |
| Formulation Vessel | T-8<br>Operating Volume of 30 - 100 L<br>Fixed Speed Mixer: 290 rpm/minute |
| Mixing Time for Addition of APIs<br>• Zinc Sulfate•7$H_2O$, USP<br>• Cupric Sulfate•5$H_2O$, USP<br>• Manganese Sulfate•$H_2O$, USP<br>• Selenious Acid, USP<br>to Initial Water for Injection Charge | NLT 10 minutes |
| Mixing Time for pH Adjustment(s) | NLT 10 minutes |
| Mixing Time (post initial Q.S.) | NLT 15 minutes |
| Mixing Time (post final Q.S.) | NLT 15 minutes |
| Bulk Holding Time | 48 hours |
| Pre-Filter | 10" Pall Profile II (Polypropylene filament) 1.0 micron<br>(ID: AB1Y0107PH4) |
| Filling Line | 1 or 3 |
| Sterilizing Filter Type, Size, and Model Number | Pall Ultipor $N_{66}$ 0.2 Micron Filter, Size 4"<br>ID: MCY4440NFPH4-4" |
| Number of Sterilizing Filters to Use | 1 |
| Filter Priming Volume | NLT 1.0 Liter |
| Receiving Vessel | 45 L Pyrex Glass Carboy |
| Container: USP Type I glass vial, Gerresheimer Gx33 | FV02T13G33 |
| Stopper: West 4432 FluroTec B2-40 | ST13WB4432FLRS |
| Fill Volume | 1 mL |
| Nitrogen Flush | No |
| Terminally Sterilized | Yes |
| Autoclave Cycle | 122.2 °C for 15 minutes |

NTL refers to not less than.

**[00250]** The compounding procedure described below was followed for a 60L batch. A 50 L USP bulk tank

(range 45 – 55 L) was charged with of water for injection (WFI). A mixer (Fixed Speed: 290 RPM) was turned on and the temperature was recorded. The mixer was turned off and specified amounts of USP Zinc Sulfate•$7H_2O$, Cupric Sulfate•$5H_2O$, Manganese Sulfate•$H_2O$ and Selenious Acid were added into the bulk tank.

**[00251]** The bulk tank was closed and mixing continued for a minimum of 10 minutes (range 10 to 15 minutes) or until dissolved. At the completion of mixing, the mixer was stopped, the tank opened, and the bulk product was visually inspected to ensure complete dissolution. Approximately 50 mL of the bulk solution was taken and checked for pH at 25°C ± 2°C. The target pH was 2.0 (range 1.9 to 2.1). If the pH of the bulk solution was not 2.0 (range 1.9 to 2.1), the pH was slowly adjusted with 10% v/v sulfuric acid solution to a target pH of 2.0 (range 1.9 to 2.1) and mixed for a minimum of 10 minutes (10 to 15 minutes) after each pH adjustment solution.

**[00252]** The mixer was turned off and the bulk solution Q.S. to 60 Liters with Water for Injection, USP. Tank was closed, and the bulk solution mixed for a minimum of 15 minutes (range 15 to 20 minutes).

**[00253]** Mixing was continued while cooling the bulk to 25 °C ± 2 °C. Mixer was turned off, the tank opened and re-verified Q.S., otherwise more water for injection USP was added, if necessary. If additional WFI, USP was added, tank was closed, and bulk solution was mixed for a minimum of 15 minutes (typical range 15 to 20 minutes). If no additional water was added, tank was closed, and this step marked as N/A. At end of mixing, the bulk tank was opened, approximately 50 mL of the bulk solution collected, and the pH checked at 25 °C ± 2 °C. Target pH was 2.0 (range 1.9 to 2.1). If the pH was not 2.0 (range 1.9 to 2.1) pH was slowly adjusted with 10% v/v sulfuric acid solution to a target pH of 2.0 (range 1.9 to 2.1). Bulk was mixed for a minimum of 10 minutes (10 to 15 minutes) after each pH adjustment solution.

**[00254]** Following the above compounding, in-process chemistry samples were taken and analyzed. The in-process results for the four exhibit batches are provided in Table 27:

**[00255]** Table 27 – In-Process Results

| **Test** | **Specifications** | **Results** | | | |
|---|---|---|---|---|---|
| | | **RD15-013** | **RD16-001** | **RD16-007** | **RD18-007** |
| Specific Gravity | Report Result | 1.009 g/mL | 1.009 g/mL | 1.009 g/mL | 1.009 g/mL |
| pH | 1.9 to 2.1 | 2.0 | 2.0 | 2.0 | 2.0 |
| Assay – Zinc | 93.0% to 107.0% | 99.5% | 102.2% | 100.8% | 99.2% |
| Assay - Copper | 93.0% to 107.0% | 101.5% | 104.7% | 103.5% | 102.2% |
| Assay - Selenium | 93.0% to 107.0% | 96.3% | 96.3% | 98.1% | 98.6% |
| Assay - Manganese | 93.0% to 107.0% | 95.9% | 99.8% | 99.1% | 99.1% |

**[00256]** Prior to transferring the bulk into the aseptic processing area (APA), a sample of the bulk solution

(approximately 100 mL) was taken and submitted to for bioburden testing. The results are provided in Table 28.

**[00257]** Table 28 – Bioburden Results

| Test | Specifications* | Results | | | |
|---|---|---|---|---|---|
| | | RD15-013 | RD16-001 | RD16-007 | RD18-007 |
| Bioburden | NMT 10 CFU/mL | < 1 CFU/mL | < 1 CFU/mL | < 1 CFU/mL | < 1 CFU/mL |

CFU refers to colony forming units.

**[00258]** A pre-use water bubble point test was performed on the sterilizing grade filter to verify the integrity of the filter. Subsequently, the bulk product was passed through a 10" 1.0 µm pre-filter and transfer line to the filling room. It was continuously filtered through one 4" 0.2 µm filter and was supplied into a sterile receiving vessel in the APA Filling Line 1 or Line 3. The filtered bulk solution was filled into 2 mL Type I, sulfur treated flint glass tubular vials with 13 mm neck openings. The filled units were then stoppered with 13 mm gray West 4432, B2-40 stoppers, and sealed with 13 mm West aluminum flip-off seals with caps. A post-filtration bubble point test was performed to check the integrity of the sterilizing-grade filter.

**[00259]** USP lots RD15-013, RD16-001, RD16-007, and RD18-007 were filled as a 1 mL fill in a 2 mL vial. Twelve consecutively filled vials were taken from the beginning, middle and end of the fill runs and gravimetrically tested to confirm fill volumes. The fill volume check sampling and results are summarized in Table 29.

**[00260]** Table 29 – Fill Volume Results

| Acceptance Criteria | Minimum: 1.16 g (1.15 mL) / Target: 1.31 g (1.3 mL) / Maximum: 1.41 g (1.4 mL) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lot # RD15-013 | | | Lot # RD16-001 | | | Lot # RD16-007 | | | Lot # RD18-007 | | |
| | Beg | Mid | End | Beg | Mid | End | Beg | Mid | End | Beg | Mid | End |
| **Average (g)** | 1.34 | 1.31 | 1.31 | 1.36 | 1.30 | 1.30 | 1.36 | 1.31 | 1.31 | 1.29 | 1.28 | 1.28 |
| Intra-lot Results | Average = 1.32 g (RSD = 2.7%) | | | Average = 1.32 g (RSD = 3.2%) | | | Average = 1.33 g (RSD = 2.3%) | | | Average = 1.28 g (RSD = 1.8%) | | |

**[00261]** Each tray of filled vials was loaded into an autoclave and the finished product was sterilized by autoclaving at 122.2ºC for 15 minutes. Following sterilization, the units were 100% inspected. A summary of the specifications and test results for the three exhibit batches and one bridging batch are provided in the Table 30.

**[00262]** Appropriate stability studies were initiated, and the required number of units of each exhibit batch were placed into storage at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH.

**[00263]** Table 30 – Release Test Results for Trace Elements Injectable Composition

| Test | Acceptance Criteria | Exhibit Batch RD15-013 | Exhibit Batch RD16-001 | Exhibit Batch RD16-007 | Bridging Batch RD18-007 |
|---|---|---|---|---|---|
| Description | Clear, colorless to slightly blue solution and is essentially free from visible particulates. | Pass | Pass | Pass | Pass |
| Identification | A. Zinc - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 472.215 nm when tested as directed for Procedure in the respective Assay. | Pass | Pass | Pass | Pass |
| | B. Copper - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 224.700 nm when tested as directed for Procedure in the respective Assay. | Pass | Pass | Pass | Pass |
| | C. Selenium - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 196.026 nm when tested as directed for Procedure in the respective Assay. | Pass | Pass | Pass | Pass |
| | D. Manganese - The Assay preparation, prepared as directed in the Assay, exhibits an emission maximum at 279.827 nm when tested as directed for Procedure in the respective Assay. | Pass | Pass | Pass | Pass |

| Test | Acceptance Criteria | Exhibit Batch RD15-013 | Exhibit Batch RD16-001 | Exhibit Batch RD16-007 | Bridging Batch RD18-007 |
|---|---|---|---|---|---|
| pH | <791> Between 1.5 and 3.5. | 2.0 | 2.0 | 2.0 | 2.0 |
| Assay | Zinc: It contains not less than 90.0% and not more than 110.0% of the labeled amount of Zn. (L.C. = 3 mg/mL of Zinc) | 99.0 % | 102.4 % | 101.7 % | 98.3 % |
| | Copper: It contains not less than 90.0% and not more than 110.0% of the labeled amount of Cu. (L.C. = 0.3 mg/mL of Copper) | 101.8 % | 103.9 % | 104.6 % | 101.5 % |
| | Manganese: It contains not less than 90.0% and not more than 110.0% of the labeled amount of Mn. (L.C. = 55 µg/mL of Manganese) | 96.6 % | 99.0 % | 99.3 % | 97.8 % |
| | Selenium: It contains not less than 90.0% and not more than 110.0% of the labeled amount of Se. (L.C. = 60 µg/mL of Selenium) | 96.3 % | 96.8 % | 98.6 % | 98.3 % |
| Residual Solvents | <467> Meets requirements under Option 2 | Meets requirements | Meets requirements | Meets requirements | Meets requirements |
| Aluminum* (GFAAS) | Not more than 6,000 µg/L. | < 1250 µg/L | < 1250 µg/L | < 1250 µg/L | < 1250 µg/L |
| Aluminum (ICP-MS) | Not more than 6,000 µg/L. | < 1880 µg/L | < 1880 µg/L | < 1880 µg/L | < 1880 µg/L |

| Test | Acceptance Criteria | Exhibit Batch RD15-013 | Exhibit Batch RD16-001 | Exhibit Batch RD16-007 | Bridging Batch RD18-007 |
|---|---|---|---|---|---|
| Elemental Impurities: | Arsenic: Not more than 1.5 µg/mL | < 0.45 µg/mL | < 0.45 µg/mL | < 0.45 µg/mL | < 0.45 µg/mL |
| | Cadmium: Not more than 0.6 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL |
| | Mercury: Not more than 0.4 µg/mL | < 0.1 µg/mL | < 0.1 µg/mL | < 0.1 µg/mL | < 0.1 µg/mL |
| | Lead: Not more than 0.5 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL | < 0.2 µg/mL |
| | Chromium: Not more than 1.0 µg/mL | < 0.3 µg/mL | < 0.3 µg/mL | < 0.3 µg/mL | < 0.3 µg/mL |
| | Iron: Not more than 10 µg/mL | < 3 µg/mL | < 3 µg/mL | < 3 µg/mL | < 3 µg/mL |
| | Silicon: Not more than 100 µg/mL | < 30 µg/mL | < 30 µg/mL | < 30 µg/mL | < 30 µg/mL |
| | Magnesium: Not more than 50 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL |
| | Calcium: Not more than 50 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL |
| | Boron: Not more than 50 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL | < 15 µg/mL |
| Volume of Solution | 1 mL vial: Not less than 1.0 mL. | 1.3 mL | 1.3 mL | 1.3 mL | 1.2 mL |
| Particulate Matter | <788> Meets requirements of the Light Obscuration Particle Count Test for small-volume injections, limits are: NMT 6,000 particles ≥ 10 µm per container NMT 600 particles ≥ 25 µm per container<br><br>If retested by the Microscopic method limits are: NMT 3,000 particles ≥ 10 µm per container NMT 300 particles ≥ 25 µm per container | 1<br><br>< 1 | 8<br><br>< 1 | 4<br><br>< 1 | 1<br><br>0 |

| Test | Acceptance Criteria | Exhibit Batch RD15-013 | Exhibit Batch RD16-001 | Exhibit Batch RD16-007 | Bridging Batch RD18-007 |
|---|---|---|---|---|---|
| Sterility | <71> If no growth is observed, the article tested meets the requirements of the test for sterility. | No growth | No growth | No growth | No growth |
| Bacterial Endotoxins | <85> The Endotoxin limit is not more than 50 EU/mL. | < 17.50 EU/mL | < 17.50 EU/mL | < 17.50 EU/mL | < 17.50 EU/mL |
| Other requirements Current USP <1> | Meets requirements | N/A | N/A | N/A | N/A |

*Aluminum was tested by both, GFAAS (graphite furnace atomic absorption spectroscopy) and ICP-MS (inductively coupled plasma mass spectrometry) methods, during the ICP-MS method development and validation.

**[00264]** Example 8 – Stability Tests

**[00265]** In this example, the trace elements injectable compositions, USP lots RD15-013, RD16-001, RD16-007, and RD18-007 were subjected to stability protocols as summarized in Table 31.

**[00266]** Table 31 – Stability Protocols

| Stability Storage Condition | Test Station (Month) |
|---|---|
| Finished Product release | Initial (0) |
| Upright 25 ± 2 °C / 60% RH ± 5% RH | 3, 6, 9, 12, 18, 24 |
| Inverted 25 ± 2 °C / 60% RH ± 5% RH | 3, 6, 9, 12, 18, 24 |
| Upright 40 ±2 °C / 75% RH ± 5% RH | 1, 3, 6 |
| Inverted 40 ±2 °C / 75% RH ± 5% RH | 1, 3, 6 |

**[00267]** From the collected data, it can be seen that after 6-month exposure to 40°C/75%RH and 24-month exposure to 25°C/60%RH conditions, all results were stable, and met the stability specifications. The stability data confirms that the manufacturing process and container closure components chosen for the manufacture of the trace elements injectable composition, USP were acceptable. Based on the results of the 24-month stability studies and acceptable 6-month accelerated stability results for the exhibit batches, we concluded that the trace elements injectable composition, USP had a 24-month expiration dating.

**[00268]** On the trace elements injectable composition of this application, we also conducted photostability studies. The stability storage conditions and exposure criteria for the drug product photostability study are summarized in the following table (Table 32) in accordance with the ICH Q1B Photostability Testing Guideline

recommendations.

**[00269]** Table 32 – Photostability Recommendations

| **Storage Condition** | **Exposure** |
|---|---|
| 25°C ± 2°C, Horizontal, Visible Light Exposure | Not less than 1.2 million lux hours |
| 25°C ± 2°C, Horizontal, Near Ultraviolet (UV) Light Exposure | Not less than 200-watt hours/$m^2$ |

**[00270]** The protocol was designed to evaluate the drug product in its immediate packaging system under light exposure by studying the following quality attributes: pH, assay, elemental impurities, description, and particulate matter. The finished product samples from the exhibit batch Lot RD15-013 were used for this study. Photostability results for the visible and UV light exposures are provided in Tables 33 and 34, respectively.

**[00271]** Table 33 – Photostability Results for Visible Light Exposure

| **Test Name** | **Specifications** | **Initial[1]** | **Shelf I** | **Shelf I-Control Wrapped Vials** |
|---|---|---|---|---|
| Visible Light Exposure | NLT 1.2 (million lux hours) | 0 | 1.36 | 1.36 |
| Description[2] | Conforms | Conforms | Conforms | Conforms |
| pH | 1.5 – 3.5 | 2.0 | 2.0 | 2.0 |
| Copper Assay | 90.0-110.0 (%) | 103.0 | 102.0 | 102.3 |
| Manganese Assay | 90.0-110.0 (%) | 97.8 | 96.8 | 97.6 |
| Zinc Assay | 90.0-110.0 (%) | 100.7 | 99.6 | 100.4 |
| Selenium Assay | 90.0-110.0 (%) | 96.5 | 97.5 | 97.3 |
| Aluminum Test (GFAA) | NMT 6000 (µg/L)[3] | < 1250 | < 1250 | < 1250 |
| Aluminum (ICP-MS) | NMT 6000 (µg/L) [3] | < 1880 | < 1880 | < 1880 |
| Silicon | NMT 100 (µg/mL) | < 30 | < 30 | < 30 |
| Magnesium | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Calcium | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Boron | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Particulate Matter 10µm | NMT 6000 (particles/container) | 1 | 3 | 1 |
| Particulate Matter 25µm | NMT 600 (particles/container) | < 1 | < 1 | < 1 |

**[00272]** Table 34 - Photostability Results for UV Light Exposure

| **Test Name** | **Specifications** | **Initial[1]** | **Shelf I** | **Shelf I-Control Wrapped Vials** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| UV Light Exposure | NLT 200 (w/m$^2$) | 0 | 422.34 | 422.34 |
| Description[2] | Conforms | Conforms | Conforms | Conforms |
| pH | 1.5 – 3.5 | 2.0 | 2.0 | 2.0 |
| Copper Assay | 90.0-110.0 (%) | 103.0 | 102.3 | 102.2 |
| Manganese Assay | 90.0-110.0 (%) | 97.8 | 96.8 | 97.1 |
| Zinc Assay | 90.0-110.0 (%) | 100.7 | 100.0 | 99.9 |
| Selenium Assay | 90.0-110.0 (%) | 96.5 | 93.5 | 94.8 |
| Aluminum Test (GFAA) | NMT 6000 (µg/L)[3] | < 1250 | < 1250 | < 1250 |
| Aluminum (ICP-MS) | NMT 6000 (µg/L)[3] | < 1880 | < 1880 | < 1880 |
| Silicon | NMT 100 (µg/mL) | < 30 | < 30 | < 30 |
| Magnesium | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Calcium | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Boron | NMT 50 (µg/mL) | < 15 | < 15 | < 15 |
| Particulate Matter 10µm | NMT 6000 (particles/container) | 1 | 1 | 1 |
| Particulate Matter 25µm | NMT 600 (particles/container) | < 1 | < 1 | < 1 |

[1] Samples not stored in the photostability chamber.
[2] Clear colorless to slightly blue solution and is essentially free from visible particulates.
[3] Limit for Aluminum was changed from 6250 µg/mL to 6000 µg/mL after completion of this study.
NMT = Not More Than
NLT = Not Less Than

**[00273]** The data from the photostability evaluation above indicated that all the test parameters met specifications thus confirming that the product was stable even after exposure to visible and/or UV lights.

Example 9 – Comparative Trace Element Compositions

**[00274]** This example shows currently available trace element compositions (e.g., Multitrace®-5 concentrated) that contain zinc, copper, selenium, manganese and chromium, which is compared to the new trace element compositions of the current application (shown in Table 35 as *, **) that have reduced amounts of zinc, copper, manganese and no detectable chromium compared to the Multitrace®-5 concentrated.

TABLE 35

| Composition | mcg/mL | | | | | Comments |
|---|---|---|---|---|---|---|
| | Zinc | Copper | Selenium | Manganese | Chromium | |
| Multitrace®-5 (Available from American Regent) | 1000 | 400 | 20 | 100 | 4 | |
| Multitrace®-5 Concentrated (Available from American Regent) | 5000 | 1000 | 60 | 500 | 10 | |
| Multitrace®-4 (Available from American Regent) | 1000 | 400 | NA | 100 | 4 | |
| Multitrace®-4 Concentrated (Available from American Regent) | 5000 | 1000 | NA | 500 | 10 | |
| Multitrace®-4 Pediatric (Available from American Regent) | 1000 | 100 | NA | 25 | 1 | |
| Multitrace®-4 Neonatal (Available from American Regent) | 1500 | 100 | NA | 25 | 0.85 | |
| ADDAMEL™ (Available from Frensenius Kabi) | 650 | 130 | 3.2 | 27 | 1 | Also contains Iodide (13 mcg), Fluoride (95 mcg), Molybdenum (1.9 mcg). |
| *New composition Adult/ Pediatric (also in Table 6) | 3000 | 300 | 60 | 55 | NA | |
| **New composition Neonatal | 1000 | 60 | 6 | 3 | NA | |

**[00275]** From the Table 35, the amount of selenium for the adult Multitrace®-5 concentrated composition and the new adult/pediatric composition is the same, which is 60 mcg/mL selenium. The other trace elements in the new adult/pediatric composition are zinc, copper, and manganese, which are in reduced amounts --mainly 3000 mcg/mL zinc, 300 mcg/mL copper, 55 mcg/mL manganese, and no detectable chromium compared to the Multitrace®-5 concentrated composition.

**[00276]** For the new neonatal composition, compared to the Multitrace®-4 neonatal composition, the zinc, copper, and manganese are in reduced amounts --mainly 1000 mcg/mL zinc, 60 mcg/mL copper, 3 mcg/mL manganese compared to the Multitrace®-4 neonatal composition. However, the selenium for the new neonatal composition is 6 mcg/mL, which is increased.

**[00277]** Both the new adult/pediatric composition and the new neonatal composition have no detectable chromium, which is unlike other commercially available compositions (e.g., Addamel™, Multitrace®-5, and Multitrace®-4).

**[00278]** These new compositions are customized to about 80% of the respective adult/pediatric and neonatal populations that need trace element additions to the parenteral nutrition. For example, the new adult/pediatric trace element composition is customized for patients above 10 kg body weight, while the new neonatal trace element composition is customized for patients under 10 kg body weight. The new adult/pediatric trace element composition and the new neonatal trace element composition will be safer than currently available trace element products.

**[00279]** Further, the adult/pediatric trace element composition when added to the KABIVEN® and CLINIMIX E admixtures and stored for up to 14 days under refrigeration (2°C to 8°C) met the protocol's acceptance criteria and showed stability in PN after 14 days under refrigeration as discussed in Examples 1-6.

**[00280]** Example 10 – Comparative Trace Element Compositions

**Table 36. Recommended Weight-Based Daily Dosage of Trace Element (mL) for Pediatric Patients weighing 10 kg to 49 kg and Corresponding Amount of Each Trace Element (mcg)**

| Body Weight | Recommended Weight-Based | Amount of Trace Element Provided by the Corresponding Trace Element Volume |
|---|---|---|

| | Dosage of Trace Element In Volume | Zinc | Copper | Manganese | Selenium |
|---|---|---|---|---|---|
| **10 kg to 19 kg** | **0.2 mL** | 600 mcg | 60 mcg | 11 mcg | 12 mcg |
| **20 kg to 29 kg** | **0.4 mL** | 1,200 mcg | 120 mcg | 22 mcg | 24 mcg |
| **30 kg to 39 kg** | **0.6 mL** | 1,800 mcg | 180 mcg | 33 mcg | 36 mcg |
| **40 kg to 49 kg** | **0.8 mL** | 2,400 mcg | 240 mcg | 44 mcg | 48 mcg |

**[00281]** Additional Supplementation with Trace Element

For pediatric patients weighing 10 kg to 49 kg, additional zinc (in heavier patients in some weight bands), copper and selenium may be needed to meet the recommended daily dosage of these trace elements, shown below. To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Trace Element (Table 36) and other dietary sources:

Zinc: 50 mcg/kg/day (up to 3,000 mcg/day)

Copper: 20 mcg/kg/day (up to 300 mcg/day)

Selenium: 2 mcg/kg/day (up to 60 mcg/day).

**[00282]** Example 11- Trace Elements Composition (Tralement™)

**[00283]** Tralement™ is indicated in adult and pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

**[00284]** The trace element composition Tralement™ can be in a single dose vial. Each mL contains zinc about 3 mg (equivalent to zinc sulfate 7.41 mg), copper about 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese about 55 mcg (equivalent to manganese sulfate 151 mcg), selenium about 60 mcg (equivalent to selenious acid 98 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

**[00285]** In some embodiments, the zinc used in the trace element composition can be zinc heptahydrate

having the molecular formula $ZnSO_4 \cdot 7H_2O$ and a molecular weight of 287.54 g/mol.

**[00286]** In some embodiments, the copper used in the trace element composition can be cupric sulfate that is in pentahydrate form having the molecular formula $CuSO_4 \cdot 5H_2O$ and a molecular weight of 249.69 g/mol.

**[00287]** In some embodiments, the manganese used in the trace element composition can be manganese sulfate that is in a monohydrate form having the molecular formula $MnSO_4 \cdot H_2O$ and a molecular weight of 169.02 g/mol.

**[00288]** In some embodiments, the selenium in the trace element composition can be selenious acid that has the molecular formula $H_2SeO_3 \cdot H_2O$ and a molecular weight of 128.97 g/mol.

Example 12 -Trace Elements Composition (Multrys ™)

**[00289]** The trace elements composition (Multrys™) is indicated in neonatal and pediatric patients weighing less than 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

**[00290]** The trace elements composition (Multrys™) can contain 4 trace elements in a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, that can be used as a combination of four trace elements and an additive to intravenous solutions for parenteral nutrition. In this particular embodiment of this example, it has no preservative. Each single-dose vial can contain 1 mL. *Each mL contains zinc about 1,000 mcg (equivalent to zinc sulfate 2,470 mcg), copper about 60 mcg (equivalent to cupric sulfate 150 mcg), manganese about 3 mcg (equivalent to manganese sulfate 8.22 mcg), selenium about 6 mcg (equivalent to selenious acid 9.8 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

**[00291]** Zinc sulfate can be in a heptahydrate form having the molecular formula: $ZnSO_4 \bullet 7H_2O$ and molecular weight of about 287.54 g/mol. The cupric sulfate can be in a pentahydrate form having the molecular formula: $CuSO_4 \bullet 5H_2O$ and molecular weight: 249.69 g/mol. The manganese sulfate can be in a monohydrate form and have the molecular formula: $MnSO_4 \bullet H_2O$ and molecular weight of about 169.02 g/mol. The selenious acid has the molecular formula: $H_2SeO_3$ and molecular weight of about 128.97 g/mol. In this particular embodiment of this example, the trace elements composition contains no more than 1,500 mcg/L of aluminum.

**[00292]** **Recommended Dosage in Pediatric Patients and Monitoring Considerations**

**[00293]** Multrys™ is a fixed-combination product. Each mL of Multrys™ provides zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg.

**[00294]** *Recommended Dosage for Pediatric Patients Weighing 0.4 kg to 0.59 kg*

The total recommended dosage of Multrys™ is 0.2 mL every other day.

Daily supplementation of Zinc, Copper, and Selenium will be needed to meet daily requirements (See Table B below).

**[00295]** *Recommended Dosage for Pediatric Patients Weighing 0.6 kg to less than 10 kg*

The recommended dosage of Multrys™ is 0.3 mL/kg/day rounded to nearest 0.1 mL for up to a maximum of 1 mL per day.

The recommended volume of Multrys™ to be added to parenteral nutrition ranges from 0.2 mL per day to 1 mL per day based on body weight, see Table A below.

**[00296]** **Table A. Recommended Daily Volume of Multrys™ and Corresponding Amount of Each Trace Element (mcg)**

| Body Weight | Recommended Daily Volume | Amount of Trace Element Provided by the Corresponding Multrys™ Volume | | | |
|---|---|---|---|---|---|
| | | Zinc mcg | Copper mcg | Manganese mcg | Selenium mcg |
| **0.6 kg to 0.8 kg** | **0.2 mL** | 200 | 12 | 0.6 | 1.2 |
| **0.9 kg to 1.1 kg** | **0.3 mL** | 300 | 18 | 0.9 | 1.8 |
| **1.2 kg to 1.4 kg** | **0.4 mL** | 400 | 24 | 1.2 | 2.4 |
| **1.5 kg to 1.7 kg** | **0.5 mL** | 500 | 30 | 1.5 | 3 |
| **1.8 kg to 2 kg** | **0.6 mL** | 600 | 36 | 1.8 | 3.6 |
| **2.1 kg to 2.3 kg** | **0.7 mL** | 700 | 42 | 2.1 | 4.2 |
| **2.4 kg to 2.6 kg** | **0.8 mL** | 800 | 48 | 2.4 | 4.8 |
| **2.7 kg to 2.9 kg** | **0.9 mL** | 900 | 54 | 2.7 | 5.4 |
| **3 kg to 9.9 kg** | **1 mL** | 1,000 | 60 | 3 | 6 |

**[00297]** *Additional Trace Element Supplementation with Multrys™*

Multrys™ is recommended only for pediatric patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese and selenium).

• To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Multrys™ and enteral nutrition sources.

**[00298]** **Table B: Daily Requirement for Trace Element Supplementation for Pediatric Patients**

| Trace Element | Patient Weight (kg) | Daily Requirement* |
|---|---|---|
| Zinc | Less than 3 kg | 400 mcg/kg/day |
| | 3 kg to 5 kg | 250 mcg/kg/day |
| | 5 to 10 kg | 100 mcg/kg/day |
| Copper | - | 20 mcg/kg/day |
| Selenium | - | 2 mcg/kg/day |
| Manganese** | - | 1 mcg/kg/day |

*Multrys™ is not recommended for pediatric patients who may require a lower dosage of one or more of these individual trace elements.

**Avoid additional manganese supplementation with Multrys™ use. Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day.

For pediatric patients weighing less than 3 kg, Multrys™ does not provide the recommended daily dosage of zinc.

Zinc: For patients weighing less than 3 kg, add Zinc Sulfate to provide total daily recommended dose of 400 mcg/kg/day using parenteral and/or enteral routes of administration.

For pediatric patients weighing 0.4 kg to 0.59 kg and 4 kg to 9.9 kg, Multrys™ does not provide the recommended daily dosage of copper or selenium.

Copper: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Cupric Chloride to provide total daily recommended dose of 20 mcg/kg/day using parenteral and/or enteral routes of administration.

Selenium: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Selenious Acid to provide total daily recommended dose of 2 mcg/kg/day using parenteral and/or enteral routes of administration.

**[00299]** Monitoring

Monitor zinc, copper, and selenium serum concentrations and manganese whole blood concentrations during long-term administration of parenteral nutrition.

**Low Chromium**

**[00300]** In some embodiments, the amount of chromium in the parenteral nutrition containing the trace elements composition (e.g., Multrys™ or Tralement™) or the trace elements composition (e.g., Multrys™ or

Tralement™) itself is not more than about 0.15 µg/mL to not more than about 0.07 µg/mL or lower. With the not more than about 0.15 µg/mL of chromium, the maximum potential exposure to chromium (e.g., 0.045 µg/kg/day) will be 22.5% of the maximum chromium dose that can be used for parenteral nutrition in a target patient population ( e.g., children (weighing 0.4 – 9.9 kg)). This can be based on a target dose volume of, for example, 0.3 mL/kg/day. In some embodiments, this will reduce the risk of toxicity from total chromium exposure in the parenteral nutrition (e.g., from intentionally added chromium and chromium as an impurity).

**[00301]** It will be apparent to those skilled in the art that various modifications and variations can be made to various embodiments described herein without departing from the spirit or scope of the teachings herein. Thus, it is intended that various embodiments cover other modifications and variations of various embodiments within the scope of the present teachings. Since modifications will be apparent to those of skill in the art, it is intended that this disclosure be limited only by the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

2. The injectable composition of claim 1, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

3. The injectable composition of claim 1, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of injectable composition.

4. The injectable composition of claim 1, further comprising (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7, aluminum from about 0.0001 to about 0.6 mcg/kg/day or a mixture thereof; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof.

5. The injectable composition of claim 1, further comprising (i) iron from about 0.0001 to about 10 µg/mL, silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron from about 0.0001 to about 50 µg/mL or a mixture thereof; (ii) iron from about 0 to about 10 µg/mL, silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof; or (iii) wherein the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection.

6. The injectable composition of claim 1, wherein the composition has a pH of about 1.0 to about 5.

7. The injectable composition of claim 6, wherein the composition further comprises a pH adjusting agent to adjust the pH.

8. The injectable composition of claim 1, wherein at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.03 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.0055 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 99.66 wt. percent based on a total weight of the injectable composition.

9. The injectable composition of claim 8, wherein at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent based on a total weight of the injectable composition.

10. The injectable composition of claim 1, wherein the injectable composition is at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition.

11. The injectable composition of claim 1, wherein the injectable composition comprises a preservative.

12. The injectable composition of claim 11, wherein the preservative comprises benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

13. The injectable composition of claim 5, wherein the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and the elemental selenium is from selenious acid.

14. The injectable composition of claim 1, wherein the injectable composition is in a multi-dose vial.

15. The injectable composition of claim 14, wherein the multi-dose vial contains 10 mL of the injectable composition.

16. The injectable composition of claim 1, wherein the injectable composition further comprises about 0.0001 µg/mL to about 0.25 µg/mL of chromium.

17. The injectable composition of claim 1, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum.

18. The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and the selenium is selenious acid at a dose of about 20 to about 60 µg/day.

19. The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.15 to about 0.8 mg/day, and the selenium is selenious acid at a dose of about 20 to about 40 µg/day.

20. The injectable composition of claim 1, wherein the injectable composition is a component of a parenteral nutrition comprising at least one of an amino acid, a dextrose, a lipid, an electrolyte, or a mixture thereof.

21. The injectable composition of claim 20, wherein at least one of (i) the amino acid comprises lysine hydrochloride, phenylalanine, leucine, valine, threonine, methionine, isoleucine, tryptophan, alanine, arginine, glycine, proline, histidine, glutamic acid, serine, aspartic acid, tyrosine or a mixture thereof; (ii) the dextrose comprises dextrose monohydrate; (iii) the lipid comprises soybean oil, phospholipid, glycerin or a mixture thereof; or (iv) the electrolyte comprises sodium acetate trihydrate, potassium chloride, sodium chloride, potassium acetate, sodium glycerophosphate anhydrous, magnesium sulfate heptahydrate, calcium chloride dihydrate, calcium gluconate or a mixture thereof.

22. The injectable composition of claim 20, wherein the pH is from about 3.5 to about 7.9.

23. The injectable composition of claim 20, wherein the composition is nonpyrogenic.

24. The injectable composition of claim 20, wherein the parenteral nutrition is stable when stored from about 2 ºC to about 8 ºC for up to about 14 days.

25. The injectable composition of claim 20, wherein the parenteral nutrition when stored from about 2 ºC to about 8 ºC for about 14 days maintains a pH from about 5.50 to about 5.90.

26. The injectable composition of claim 20, wherein the parenteral nutrition when stored from about 2 ºC to about 8 ºC for about 14 days comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm.

27. The injectable composition of claim 20, wherein the parenteral nutrition further comprises aluminum in an amount from about 0.0001 to about 6 µg/mL or not to exceed 6 µg/mL.

28. The injectable composition of claim 20, wherein the parenteral nutrition when stored from about 2 ºC to about 8 ºC for about 14 days did not exhibit microbial growth.

29. The injectable composition of claim 27, wherein the microbes comprise *S. aureus, P. aeruginosa, E. coli*, *C. albicans*, *A. brasiliensis* or a mixture thereof.

30. The injectable composition of claim 1, wherein the injectable composition is disposed in a container.

31. The injectable composition of claim 30, wherein the container comprises a single use vial or ampule or the container comprises a vial having a stopper and/or a cap.

32. The injectable composition of claim 31, wherein the vial or ampule comprises Type I glass or plastic.

33. An injectable composition comprising water, and trace elements consisting of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

34. The injectable composition of claim 33, wherein the trace elements consist of 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

35. The injectable composition of claim 33, wherein the trace elements consist of 1,000 µg of zinc, 60 µg of copper, 6 µg of selenium, and 3 µg of manganese per 1 mL of the injectable composition.

36. The injectable composition of claim 33, wherein the trace elements consist of zinc sulfate or zinc sulfate heptahydrate in an amount of about 13.1 mg to about 13.3 mg, cupric sulfate or cupric sulfate pentahydrate in an amount of about 1.1 mg to about 1.2 mg, manganese sulfate or manganese sulfate monohydrate in an amount of about 0.16 mg to about 0.18 mg and selenious acid in an amount of about 95 µg to about 99 µg per 1 mL of the injectable composition.

37. The injectable composition of claim 33, wherein the trace elements consist of zinc sulfate or zinc sulfate heptahydrate in an amount of about 13.1 mg to about 13.3 mg, cupric sulfate or cupric sulfate pentahydrate in an amount of about 1.1 mg to about 1.2 mg, manganese sulfate or manganese sulfate monohydrate in an amount of about 0.016 mg to about 0.018 mg and selenious acid in an amount of about 95 µg to about 99 µg per 1 mL of the injectable composition.

38. The injectable composition of claim 36, wherein the zinc sulfate or zinc sulfate heptahydrate is in an amount of about 13.2 mg, the cupric sulfate or the cupric sulfate pentahydrate is in an amount of about 1.179 mg, the manganese sulfate or manganese sulfate monohydrate is in an amount of about 0.169 mg and the selenious acid is in an amount of about 98 µg per 1 mL of the injectable composition.

39. A method of making an injectable composition, the method comprising mixing at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about

90 µg of selenium, or about 1 µg to about 80 µg of manganese with water to form 1 mL of the injectable composition.

40. The method of claim 39, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

41. The method of claim 39, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per about 250 mL to 4000 mL of parenteral nutrition.

42. The method of claim 39, wherein the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection.

43. The method of claim 39, wherein the composition has a pH of about 1.2 to about 5.

44. The method of claim 43, wherein the composition further comprises at least sodium hydroxide or sulfuric acid to adjust the pH.

45. The method of claim 39, wherein at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.05 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.026 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 98.5 wt. percent based on a total weight of the injectable composition.

46. The method of claim 39, wherein the injectable composition is at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition.

47. The method of claim 39, wherein the injectable composition comprises a preservative.

48. The method of claim 47, wherein the preservative comprises benzyl alcohol in an amount of 0.9

% by weight based on a total weight of the injectable composition.

49. The method of claim 42, wherein the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and the elemental selenium is from selenious acid.

50. The method of claim 39, wherein the injectable composition is in a multi-dose vial.

51. The method of claim 50, wherein the multi-dose vial contains 10 mL of the injectable composition.

52. The method of claim 39, wherein the injectable composition further comprises about 0.00001 µg/mL to about 0.25 µg/mL of chromium.

53. The method of claim 39, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum.

54. The method of claim 39, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.15 to about 0.8 mg/day, and the selenium is selenious acid at a dose of about 20 to about 40 µg/day.

55. The method of claim 39, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and the selenium is selenious acid at a dose of about 20 to about 40 µg/day.

56. A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about

400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

57. The method of claim 56, wherein the injectable composition when stored from about 2 ºC to about 8 ºC for about 14 days comprises at least one of (i) no more than 12 particle per mL that are greater than 10 µm; or (ii) no more than 2 particle per mL that are greater than 25 µm.

58. The method of claim 56, wherein the injectable composition when stored from about 2 ºC to about 8 ºC for about 14 days did not exhibit microbial growth.

59. The method of claim 58, wherein the microbes comprise *S. aureus, P. aeruginosa, E. coli*, *C. albicans*, *A. brasiliensis* or a mixture thereof.

60. The method of claim 56, wherein the injectable composition when stored from about 2 ºC to about 8 ºC for about 14 days maintains a pH from about 5.50 to about 5.90.

61. The method of claim 56, further comprising treating patients having a negative nitrogen balance.

62. The method of claim 56, further comprising use of the electrolyte as a supplement to intravenous solutions given for parenteral nutrition to maintain plasma levels of zinc, copper, manganese and selenium to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

63. The injectable composition of claims 1-38, wherein the injectable composition is administered to a human patient.

64. The method of claim 39-62, wherein the injectable composition is administered to a human patient.

65. An injectable trace element composition comprising water, about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg

to about 80 µg of manganese per 1 mL of the injectable composition.

66. The injectable composition of claim 1, wherein zinc comprises from about 800 µg to about 4000 µg per 1mL of the injectable composition.

67. The injectable composition of claim 1, wherein copper comprises from about 40 µg to about 400 µg per 1mL of the injectable composition.

68. The injectable composition of claim 1, wherein selenium comprises from about 4 µg to about 90 µg per 1mL of the injectable composition.

69. The injectable composition of claim 1, wherein manganese comprises from about 1 µg to about 80 µg per 1mL of the injectable composition.

70. The injectable composition of claim 1, wherein the zinc, copper, selenium, manganese are in elemental or salt form.

71. The injectable composition of claim 7, wherein the pH adjusting agent is at least sodium hydroxide or sulfuric acid.

72. A method of maintaining, supplementing or increasing one or more trace elements to a patient in need thereof, the method comprising administering to the patient about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per about 250 mL to 4000 mL of aqueous fluid, the aqueous fluid comprising an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof.

73. The injectable composition of claim 1, wherein the injectable composition comprises elemental zinc to elemental copper in a ratio from about 100:1, 80:1, 70:1, 60:1, 50:1, 30:1, 20:1, 15:1, 10:1, 5:1, 2.5:1 to about 2:1; elemental zinc to elemental manganese in a ratio from about 4000:1, 3,000:1, 2,000:1, 1,000:1, 500:1, 200:1, 100:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15;1, 10:1 to about 5:1; elemental zinc to elemental selenium in a ratio from about 1000:1, 500:1, 200:1, 100:1, 90:1,

85:1, 83.3:1, 80:1, 75:1, 70:1, 65:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15:1, 10:1 to about 9:1; elemental copper to elemental selenium in a ratio from about 100:1, 50:1, 20:1, 15:1, 10:1, 5:1, 3:1, 2:1, 1:1 to about 0.4:1; elemental copper to elemental manganese in a ratio from about 400:1, 300:1, 200:1, 100:1, 90:1, 85:1, 80:1, 75:1, 70:1, 65:1, 60:1, 55:1, 50:1, 45:1, 40:1, 35:1, 30:1, 25:1, 20:1, 15:1, 10:1, 5.5:1, 5:1, 2.5:1, 2:1, 1:1 to about 0.5:1; and/or elemental selenium to elemental manganese in a ratio from about 100:1, 90:1, 75:1, 50:1, 30:1, 20:1, 10:1, 5:1, 3;1, 2:1, 1.1:1, 1:1, 0.5:1, 0.4:1 to about 0.05:1.

74. The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium.

75. The injectable composition of claim 1, wherein the permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

ABSTRACT

Injectable compositions that can be added to parenteral nutrition are provided. In particular, a stable injectable composition is provided which includes water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, from about 4 µg to about 90 µg of selenium, or from about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition. Methods of preparing and using of the stable injectable composition are also provided.

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/124,391 | 03/21/2023 | Gopal Anyarambhatla | 1848-32-CON-TRK1 | 3879 |

109802 7590 09/13/2023

Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

| EXAMINER | |
|---|---|
| SOROUSH, ALI | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/13/2023 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mtorres@slsllp.com
npinou@slsllp.com
wschmidt@slsllp.com

# Office Action Summary

| Application No. | Applicant(s) | | |
|---|---|---|---|
| 18/124,391 | Anyarambhatla et al. | | |
| **Examiner** | **Art Unit** | **AIA (FITF) Status** | |
| ALI SOROUSH | 1617 | Yes | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 08/23/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1-6,8-9,11,13-19,56,63-70 and 74-77 is/are pending in the application.

5a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-6,8-9,11,13-19,63,65-70 and 74-77 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 03212023 and 05052023.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Continuation of Disposition of Claims* 5a) Of the above claim(s) is/are withdrawn from consideration: 56 and 64

## DETAILED ACTION

### *Notice of Pre-AIA or AIA Status*

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

### *Acknowledgement of Receipt*

Applicant's response filed on 08/23/2023 to the Office Action mailed on 06/23/2023 is acknowledged.

### *Claim Status*

Claims 1-6, 8, 9, 11, 13-19, 56, 63-70, and 74-77 are pending.

Claims 7, 10, 12, 20-55, 57-62, and 71-73 were previously cancelled.

Claims 56 and 64 are withdrawn as being directed to a non-elected invention.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-77 have been examined.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-77 are rejected.

### *Election/Restrictions*

Applicant's election without traverse of Group I (claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-77) in the reply filed on 08/23/2023 is acknowledged.

### *Priority*

Priority to CON 17/365,695 filed on 07/01/2012, which claims priority to application 63/047,708 filed on 07/02/2020.

***Information Disclosure Statement***

The information disclosure statements (IDSs) submitted on 03/21/2023 and 05/05/2023 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

***Claim Rejections - 35 USC § 112***

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-77 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

The term “about” in claims 1-6, 8, 9, 11, 16-18, and 74-77 is a relative term which renders the claim indefinite. The term “about” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 13, 14, 15, 19, 63, and 65-70 are rejected for being dependent directly or indirectly claim 1 which is indefinite and includes all the limitations thereof.

***Claim Rejections - 35 USC § 102***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claim(s) 1, 6, 8, 13, 16, 18, 19, 66, 69, 70, 74, and 75 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Selepen (Selenium IV Additive for use with TPN, Published 01/15/2008) as evidenced by Poole et al. (Aluminum Exposure in Neonatal Patients Using the Least Contaminated Parenteral Nutrition Solution Products, Published 11/02/2012).

Selepen with regard to claim 1 teaches selepen is a sterile solution consisting of 40 µg/ml (with regard to claims 8 and 18) selenium (as selenious acid (with regard to claims 13 and 19)), water for injection, a pH of approximately 2.0 (with regard to claim 6) adjusted with nitric acid (with regard to claims 66 and 70) (page 2, description). The single dose preparation is in a 10ml flip-top vial (with regard to claim 69) (page 6, availability of dosage forms). With regard to limitations of claims 1 and 74 directed to the amount of chromium and iron, Selepen does not teach or suggest that there is any chromium or iron in the composition, which reads on the instant limitations. With regard to the limitations of claims 1 and 4 directed to the amount of

aluminum, Poole et al. teach that the amount of aluminum in a composition that includes the same ingredients as Selepen composition comprises 0.285µg/ml aluminum as a contaminant (page 1570, Table 3). For the foregoing reasons the instant claims are anticipated by the prior art.

Claim(s) 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, 74, 75, and 76 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017).

American Regent with regard to claim 1 teach a sterile injectable solution consisting of 60 µg selenium (as 98µg selenious acid), water, and nitric acid having a pH of 1.8-2.4 in a 10ml vial and has an aluminum content of not more than 2.5µg/ml (page 7, Description). Pluhator-Murton et al. teach that total parenteral nutrition solutions comprise chromium and aluminum as contaminants (abstract). Menendez et al. teach iron is a known contaminant of total parenteral nutrition solution (abstract). With regard to the amounts of aluminum, chromium, and iron, the Examiner notes that the composition of American Regent is identical to the instantly claimed composition and that aluminum, chromium, and iron are known as contaminants in the compositions such as the American Regent composition. Therefore, it would be expected that the composition of American Regent inherently comprises the same amounts of aluminum, chromium, and iron as contaminants. For the foregoing reasons the instant claims are anticipated by the prior art.

***Claim Rejections - 35 USC § 103***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claim(s) 3, 11, 15, 68, and 77 is/are rejected under 35 U.S.C. 103 as being unpatentable over American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017), as applied to claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, 74, 75, and 76 above.

The teachings of American Regent, Pluhator-Murton et al., and Menendez et al. are discussed above.

American Regent does not expressly teach a composition comprising 6µg/ml selenium and/or 9.8µg/ml of selenious acid. However, American Regent renders such a composition obvious.

It would have been prima facie obvious to one of ordinary skill in the art at the time of effective filing date of the instant invention to dilute the composition of American Regent to arrive at the instant amount and have a reasonable expectation of success. One would have been motivated to do so through routine optimization of the composition for a particular patient in view of their age, gender, and/or weight. For the foregoing reasons the instant claims are rendered obvious by the teachings of the prior art.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

**PATENT**
**(1848-32 CON TRK 1)**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | American Regent, Inc. | Examiner: | SOROUSH, ALI |
| Serial No: | 18/124,391 | Art Unit: | 1617 |
| Filed: | March 21, 2023 | Conf. No.: | 3879 |
| For: | TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE | | |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

**DECLARATION OF MS. JOANN GIOIA UNDER 37 C.F.R. § 1.132**

I, Joann Gioia, declare that:

1. I am Vice President and Chief Commercial Officer at American Regent, Inc. (American Regent) and have been in this role since February 2021. Prior to this role, from February 2020 to February 2021, I was Associate Vice President of Commercial Operations and National Accounts at American Regent. The current assignee of the above patent application.

2. I attended Katherine Gibbs and Suffolk Community College and studied Business Administration from 1987-1990.

3. I have over 25 years of experience in the pharmaceutical industry in general management, commercial operations, and alliance management in both multisource generics, single source generics, and injectable trace element and iron products. I am familiar with the commercial sales and marketing of the single trace element selenium products. A copy of my curriculum vitae is attached as Exhibit I.

**Selenium 60 µg per 1 mL and Selenium 6 µg per 1 mL Nexus to the Current Claims**

4. I have been advised that one way to establish that the claimed invention is not obvious is to show that the claimed invention has commercial success and that there is a connection or nexus between that commercial success and the claimed invention.

5. Let me briefly discuss the new single trace element selenium 60 µg per 1 mL product and the new single trace element selenium 6 µg per 1 mL product that, it is my understanding, are claimed in the above patent application. These single trace element selenium products have unique strengths per 1 mL of injectable solution not found in other single trace element products. They also have no chromium, aluminum, fluoride or iodine or very little chromium, aluminum, fluoride, or iodine as contaminants or impurities. The selenium 60 µg per 1 mL product can be used in adult and pediatric patients, and the selenium 6 µg per 1 mL product can be used in pediatric and neonatal patients.

6. Both the selenium 60 µg per 1 mL product and the selenium 6 µg per 1 mL product were the first FDA approved single active ingredient selenium products for safe and effective selenium supplementation for a majority of adult, pediatric and/or neonatal patients. (See Exhibit D and Exhibit E- American Regent FDA announcements). Both selenium single trace element products are currently on sale in the market and widely used throughout the United States.

7. Table A below shows the connection or nexus of, for example, claim 1 to the selenium 60 µg per 1 mL product. As you can see, the single active ingredient is selenium 60 µg and there is no chromium, aluminum, fluoride, iron or low amounts of these impurities in this product.

**Table A**

| **Active Ingredient per 1 mL FDA Approved Product Adult and Pediatric Patients** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 60 µg | Selenium about 60 µg |
| | |
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.3 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

8. Table B below shows the connection or nexus of, for example, claim 1 to the selenium 6 µg per 1 mL product. As you can see, the single active ingredient is selenium 6 µg and there is no chromium, aluminum, fluoride, iron or low amounts of these impurities in this product.

**Table B**

| **Active Ingredient per 1 mL FDA Approved Product Pediatric And Neonatal Patients Less Than 7 Kilograms** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 6 µg | Selenium about 6 µg |
| | |
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.0045 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

**Commercial Success**

9. Prior to the manufacturing of the above selenium 60 µg or 6 µg per 1 mL products, there were products available at different times in the United States, but these products had selenium as the single active ingredient at 40 µg per 1 mL and these products were not FDA approved. These products were made by American Regent. They were also made by Selepen (Exhibit S), which is mentioned by the Examiner in the Office Action. After their FDA approval and launch, the selenium 60 µg or 6 µg per 1 mL single trace element products became widely used throughout the United States and have been very commercially successful.

10. For example, the selenium 60 µg/mL product (e.g., for adult use) was launched on July 10, 2019 (Exhibit F) and had over $39 million in direct sales in 2019. In 2020, the direct sales of the selenium 60 µg/mL product increased to over $93 million and in 2021, the direct sales continued to increase to over $111 million. In 2022, the direct sales were $87 million, which is lower but this was in a large part due to the availability of the selenium 6 µg/mL product (e.g., for neonatal use).

11. Regarding the selenium 6 µg/mL product (e.g., for neonatal use), it launched on March 31, 2022 (Exhibit E) and had over $200 million in direct sales for 2022. Moreover, the commercial success was not due to any significant marketing effort by American Regent.

12. The commercial success of these products stems from the products themselves described in, for example, claim 1. The commercial success is not due to any significant marketing effort by American Regent. This is further evidenced by our limited budget of under $500,000 spent on marketing the selenium products after their launch.

13. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. All statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Joann Gioia
Ms. Joann Gioia

12/13/2023
Date

# Joann Gioia

EXHIBIT I

## Contact

2837 Pine Avenue

(631)645-3807
joanngc@verizon.net

## Key Skills

Opportunity Analysis
Sales Operations
Long Term Value Creation
Multi-Year Business Plans
Talent Development
Leadership

## Profile

25+ Years Generic/Branded Injectable Pharmaceutical Experience. Designed and developed dynamic marketing strategies expanding growth positioning of our brands as #1 & #2 in their shared market. Developed long -term contracting strategies for generic injectables expanding their life cycle

## Experience

*February 2021-Present*
VP, Chief Commercial Officer
American Regent
Member of the Executive Leadership Team, provides leadership, strategic vision, and functional expertise required to lead the company to commercial success. Leads the marketing, market access, commercial analytics, forecasting, new product planning and portfolio strategy teams.

*Other American Regent Experience:*
February 2020-February 2021 – AVP Commercial Operations
2017-2020 – Sr. Director Commercial Operations
2014-2016 – Director of Corporate Accounts
2011-2013 – Director of Contracts, Pricing, and Analytics
2008-2010 – Associate Director of Contracts/Chargebacks
2005-2007 – Mgr of Contracts/Chargebacks/Government Reporting
1996-2004 – Contracts Supervisor, Contract Associate

1993-1996 – Minolta Business System, Melville, NY
Sales Administration

## Education

*1989-1990*
Suffolk Community College
Business Administration

*1987-1989*
Katherine Gibbs
Business Administration

1987
Connetquot High School

**PATENT**
**(1848-32 CON TRK 1)**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | American Regent, Inc. | Examiner: | ALI SOROUSH |
| Serial No: | 18/124,391 | Art Unit: | 1617 |
| Filed: | March 21, 2023 | Conf. No.: | 3879 |
| For: | TRACE ELEMENT COMPOSITIONS METHODS MAKING AND USE | | |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

**DECLARATION OF RICHARD P. LAWRENCE UNDER 37 C.F.R. 1.130(a) AND UNDER 37 C.F.R. § 1.132**

I, Richard P. Lawrence, declare that:

1. I have been employed since 1983 at American Regent, Inc. (formerly Luitpold Pharmaceuticals, Inc.), which is the current assignee of the above-identified application.

2. I am currently the Director of Technical Services at American Regent, Inc. and am an inventor of the above-identified patent application (our patent application).

3. A brief overview of my qualifications and experience is attached as Exhibit A.

4. I submit this declaration based upon my training, knowledge, education, and experience of more than 40 years in the field of injectable trace elements used in parenteral nutrition products.

5. I have reviewed the file history of our patent application in this case including, among other things, the September 13, 2023 Office Action (Office Action); Selenium IV Additive for use with TPN, Published 01/15/2008 (Selepen-Exhibit S); Aluminum Exposure in Neonatal Patients Using the Least Contaminated Parenteral Nutrition Solution Products, Published 11/02/2012 (Poole-Exhibit P); Selenious Acid Injection that was revised April 2019 (American Regent Label); Trace Element Contamination of Total Parenteral Nutrition. Contribution of Component Solutions, Published 1999 (Pluhator-Murton-Exhibit H); and Iron contamination in parenteral nutrition mixtures, Published 11/14/2017 (Menendez-Exhibit G).

6. I disagree with the Examiner's comments in the Office Action that our patent application is disclosed or made obvious by Selepen, Poole, the American Regent Label, Pluhator-Murton and Menendez.

**Our New and FDA Approved Selenium Finished Products Are Not Obvious**

7. Our patent application is directed to, among other things, new injectable selenium single trace element finished products, where the selenium can be at a concentration of 60 µg per 1 mL for adults and pediatric patients or at a concentration of 6 µg per 1 mL for pediatric and neonatal patients under 7 kilograms. We recognized that, among other things, the selenium can be a source of impurities. Our injectable selenium finished products are highly pure and contain no chromium, no aluminum, no iron, no fluoride or low amounts of chromium, aluminum, iron and/or fluoride as impurities as described in Tables 2, 4 and 30, paragraph [0087] and originally filed claims 4 and 63 of our patent application. The new selenium finished products containing 6 µg or 60 µg of selenium per 1 mL were the first FDA approved selenium products for safe and effective supplementation for a majority of adult, pediatric and/or neonatal patients. (See Exhibits D and E- American Regent FDA announcements). Our new selenium products maintained their potency of between 90% to 110% of that which was indicated on the label. See our patent application at, for example, at Page 70, Table 30.

8. Our new and FDA approved selenium injectable finished products containing 60 µg or 6 µg of selenium per 1 mL were difficult to develop and not obvious to do so. The new selenium finished products that we developed were more than just testing for contaminants. The finished products we developed had no or very low levels of impurities that were difficult to detect, if at all, at the upper and lower limits we set. We even had to develop specialized tests and instruments including coupled plasma mass spectrometry (ICP-MS) with validated limits of quantification to detect and make sure our impurities, if any, were at no detectable levels or very low levels.

9. More particularly, during manufacturing of our new and FDA approved selenium finished products, we recognized that in addition to the drug substance, selenious acid, the drug product manufacturing process, equipment and container/closure components can be a source of impurities. Therefore, we needed to make sure no chromium, iron, fluoride, iodine, and/or silicon or very low amounts of these were not above our established permitted daily limits (PDL) and our new control thresholds for impurities. These impurities can enter the selenium finished product during manufacture from, for example, the active selenium ingredient, excipients, stopper, vial, mixing vessels, filter, water, air, etc. These new selenium finished products are manufactured within our new control thresholds of less than 30% of our established PDL limits compared to existing unapproved selenium products.

10. For example, when developing the new selenium 60 µg per 1 mL finished product for adult and pediatric patients, we had to make a more concentrated selenium 60 µg per 1 mL product that did not exist. The previously marketed selenium products at that time were not FDA approved and were at a lower concentration, such as for example, 40 µg per 1 mL (Selepen Product – Exhibit S) or American Regent's earlier selenium 40 µg per 1 mL product (Exhibit T). If we took, for example, the old Selepen Product of 40 µg per 1 mL to design a new 60 µg selenium product, we would have to use 1.5 mL of the old Selepen Product. With this increased volume of 1.5 mL to obtain 60 µg of selenium, we would have higher amounts of impurities in the finished product due to the larger volume that would not be approved by the FDA today.

11. Also, increasing the concentration of a selenium product can lead to the introduction of

higher concentrations of impurities and thus particular attention had to be given to our new selenium 60 µg per 1 mL finished product to limit the amounts of chromium, aluminum, fluoride, silicon, potassium, magnesium, sodium and/or calcium using our new established control thresholds so that the finished product was suitable for use in adult and pediatric patients. The 60 µg of selenium per 1 mL finished product provides the clinician with an easy and more accurate way of supplementing selenium by, often times, measuring a 1 mL dose of the 60 µg per 1 mL selenium product to supplement adult and pediatric patients.

12. Table C below illustrates some of the elemental impurities and ranges that we had to keep below in the new selenium and FDA approved finished product of 60 µg per 1 mL that was suitable for use in adult and pediatric patients. We could not go above certain permitted daily limits in this patient population. The low impurity levels are not disclosed and are not made obvious by the references mentioned in the Office Action.

**Table C**
**Some Elemental Impurities for Selenium Injection, USP 60 µg/mL**
**Adult and Pediatric Patients**

| Element | Concentration Limit (µg/mL) | Control Threshold (µg/mL) | Lot Number* | | |
|---|---|---|---|---|---|
| | | | 9118 (µg/mL) | 9125 (µg/mL) | 9133 (µg/mL) |
| Cr (Chromium) | 1.0 | 0.3 | <0.3 | <0.3 | <0.3 |
| Al (Aluminum) | 2.5 | 0.75 | <0.75 | <0.75 | <0.75 |
| Fe (Iron) | 10 | 3 | <3 | <3 | <3 |
| Si (Silicon) | 100 | 30 | <30 | <30 | <30 |
| I (Iodine) | 30 | 9 | <0.005 | <0.005 | <0.005 |
| Fluoride | 15 | 4.5 | <0.125 | <0.125 | <0.125 |
| K (Potassium) | 94000 | 28200 | <30 | <30 | <30 |
| Mg (Magnesium) | 50 | 15 | <15 | <15 | <15 |
| Na (Sodium) | 24000 | 7200 | <30 | <30 | <30 |
| Ca (Calcium) | 50 | 15 | <15 | <15 | <15 |

13. For pediatric and neonatal patients weighing less than 7 kilograms, we developed the new selenium finished product containing 6 µg per 1 mL, which would also not be obvious. The concentration of 6 µg of selenium per 1 mL did not exist before the current application and particular attention was given to limit the amounts of chromium, aluminum, fluoride, silicon,

potassium, magnesium, sodium and/or calcium and other impurities in the finished product so that it could supplement the selenium needs of pediatric and neonatal patients that weigh less than 7 kilograms. The 6 µg of selenium per 1 mL finished product provides the clinician an easy and more accurate way of supplementing selenium by, often times, injecting a 1 mL dose of the composition as opposed to measuring a 0.1 mL dose of the more concentrated 60 µg of selenium for neonatal and/or pediatric patients. The larger volume of the 6 µg of selenium per 1 mL allows less selenium to be lost, for example, in the IV tube set and/or IV bag especially when supplementing selenium in neonatal or pediatric patients.

14. During manufacture of our new and FDA approved selenium finished product having 6 µg per 1 mL for pediatric and neonatal patients weighing less than 7 kilograms, we also had to keep the impurity levels very low as shown in Table D below so as to not go above certain permitted daily limits for this patient specific population. For example, the new and FDA approved selenium 6 µg per 1 mL injection finished product for pediatric and neonatal patients had chromium levels below 0.0045 µg/mL, which is almost 67 times lower than the below 0.3 µg/mL of the more concentrated selenium 60 µg per 1 mL product shown in Table C above. These low levels for both finished products are not disclosed and are not made obvious by the references mentioned in the Office Action.

**Table D**
**Some Elemental Impurities for Selenium Injection, USP 6 µg/mL**
**Pediatric And Neonatal Patients Weighing Less Than 7 Kilograms**

| Element | Concentration Limit (µg/mL) | Control Threshold (µg/mL) | Lot Number* | | |
|---|---|---|---|---|---|
| | | | RD19-029 (µg/mL) | RD19-030 (µg/mL) | RD19-031 (µg/mL) |
| Cr (Chromium) | 0.015 | 0.0045 | <0.0045 | <0.0045 | <0.0045 |
| Al (Aluminum) | 0.9 | N/A | <0.75 | <0.75 | <0.75 |
| Fe (Iron) | 10 | 3 | <3 | <3 | <3 |
| Si (Silicon) | 100 | 30 | <30 | <30 | <30 |
| I (Iodine) | 1.5 | 0.45 | <0.005 | <0.005 | <0.005 |
| Fluoride | 0.75 | 0.225 | <0.125 | <0.125 | <0.125 |
| K (Potassium) | 47000 | 14100 | <30 | <30 | <30 |
| Mg (Magnesium) | 50 | 15 | <15 | <15 | <15 |
| Na (Sodium) | 12000 | 3600 | <30 | <30 | <30 |
| Ca (Calcium) | 50 | 15 | <15 | <15 | <15 |

15. In both the new and FDA approved selenium finished 6 µg or 60 µg per 1 mL products, we appreciated the fact that the selenium finished product could be the source of impurities such as, for example, at least fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium and none of the cited references mention that selenium can be a source of at least fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium impurities.

**Lower Bacterial Endotoxin Limits For Safer Selenium Supplementation**

16. Injectable pharmaceutical products are tested for the presence of endotoxins in what is called a Bacterial Endotoxins Test (BET). The BET is an *in vitro* assay for detection and quantitation of bacterial endotoxins that can be a component of the cell wall of gram-negative bacteria. Bacteria shed endotoxins upon cell death and when they are actively growing. If endotoxins are present in the injectable product, they can lead to a pyrogenic response (e.g., contaminants that can cause a fever) or sepsis in a patient. Typically, endotoxins are measured in Endotoxin Units per milliliter (EU/mL) as described in Tables 2 and 30 of the current patent application.

17. In our new and FDA approved selenium 6 µg or 60 µg per 1 mL finished products, we had to use very pure components that would be safer and have lower BET limits. For our new and FDA approved more concentrated 60 µg per 1 mL selenium finished product, we had to meet more stringent BET limits of NMT 50 EU/mL, which indicates a safer finished product. The unapproved older selenium 40 µg per 1 mL finished product did not have to meet such stringent BET requirements.

18. For our new and FDA approved lower concentration of 6 µg per 1 mL selenium finished product that is suitable for use in pediatric and neonatal patients under 7 kilograms, during manufacturing we had to reduce the concentration of selenium to 6 µg per 1 mL in the finished product and limit the introduction of impurities into the finished product by improving the quality of raw materials used to make the finished product. For example, we had to use more water during manufacturing and had to make sure the water had no or reduced impurities. Aluminum, chromium, fluoride and iodine can accumulate in, for example, neonatal patients, and we were very conscious of the particular upper limits of these impurities. We also had to meet more stringent BET limits of NMT 17.5 EU/mL, in order for our new selenium finished product to be safer and FDA approved for use in pediatric and neonatal patients that weight less than 7 kilograms. The unapproved older selenium 40 µg per 1 mL (e.g., Selepen Product) did not have to meet such stringent BET requirements and you would need 0.15 mL to have a dose of 6 µg, which was not easy for the clinician to administer such a small volume accurately.

**Selepen's Label**

19. In the Office Action, the Examiner mentions Selepen's label to say our patent application is unpatentable. Although Selepen's label mentions selenium 40 µg/mL for injection that contains sterile water, nitric acid and has a pH of approximately 2, I cannot find the impurities listed on the label. Selepen's label provides information on an old unapproved selenium 40 µg/mL product. Selepen's label, which among other impurities does not disclose and does not make obvious that selenium can be a source of impurities such as, for example, chromium, aluminum, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium. In all

my more than 40 years of experience working with selenium trace element products, impurities such as chromium, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium were not displayed on any label. Thus, there is no way for a person of ordinary skill in the art to determine just from Selepen's label alone what impurities are in the finished product. One would need to analyze the finished product as the finished product including impurities is not identified on the label. Therefore, I disagree with the Examiner's position that a person of ordinary skill in the art would assume that there is no chromium or iron in the finished product as the Examiner mentions on Page 4 of the Office Action.

**Poole**

20. In the Office Action, Poole is discussed as being concerned with neonatal patients receiving too much aluminum impurities from certain parenteral nutrition components including, for example, amino acids, dextrose, lipids, and electrolytes listed in Table 1 and certain trace element products listed in Table 3 below. The Examiner discusses that our patent application is unpatentable because Poole mentions that the aluminum content is 0.285 µg/mL in a product "similar to" Selepen, and the Examiner appears to incorrectly substitute Selepen's label, with American Regent's older selenium product, which has an aluminum content, as measured by Poole, within the range we have claimed of not exceeding 6 µg/mL in our patent application (see the Office Action at Page 5). I respectfully disagree with the Examiner and do not understand why Selepen's selenium product is compared to American Regent's old unapproved selenium product other than the fact they both contain 40 µg/mL per 1 mL of selenium. Otherwise, these are completely different products.

21. More particularly, on reading Table 3 of Poole, which is reproduced below, Poole is testing American Regent's old and unapproved selenium 40 µg/mL product (as indicated by the arrow below) and not Selepen's product.

Table 3

Aluminum content of trace elements and multivitamins used in parenteral nutrition solutions. Reprinted with permission from [1].

| | Manufacturer (NDC) | Days from Expiry (Range) | Mean Al Content (µg/L) | | |
|---|---|---|---|---|---|
| | | | Labeled | Measured (Range) | p-Value |
| Zinc Chloride (1 mg/mL) | *Hospira (0409-4090-01)* | *411 (386-451)* | *150* | *11 (5-18)* | *0.0067* |
| | American Regent (0517-6110-25) | 604 (568-635) | 2500 | 249 (54-359) | 0.002 |
| Selenium (40 µg/mL) | *American Regent (0517-6510-25)* | *481 (386-549)* | *2500* | *285 (186-399)* | *0.008* |
| Pediatric trace elements | *American Regent Multitrace-4 (0517-9310-25)* | *518 (518) ** | *2500* | *161 (161) ** | *NS* |
| | American Regent Pediatric Trace Elements (0517-9203-25) | 462 (386-518) | 5000 | 574 (316-739) | 0.0069 |
| Pediatric multivitamin | Baxter (34643-5647-0) | 261 (239-306) | 30 | 28 (26-29) | 0.1 |
| | *Hospira (61703-421-33)* | *99 (56-123)* | *42* | *18 (14-25)* | *0.02* |

NDC, National Drug Code; *Italics*: least aluminum content and used in patient database; * only one lot was sampled for this product.

22. Moreover, Selepen's product is not "similar to" American Regent's older unapproved

product as Selepen's product can contain benzyl alcohol, which is potentially toxic to neonatal patients as it can accumulate in their organs due to their metabolic immaturity and may cause fatal reactions. Therefore, to me, Selepen and Poole are incompatible with each other and I do not understand why they are being discussed as similar.

23. Regarding American Regent's unapproved older 40 µg per 1 mL selenium product, the label warns about aluminum toxicity but does not discuss any upper or lower limits to the aluminum toxicity (see Exhibit T). The new and FDA approved selenium finished products of 6 µg or 60 µg per 1 mL are also at a different concentration than the older American Regent product mentioned in Poole. Further, in both Poole and Selepen, there is no discussion of impurities such as chromium, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium and both Selepen and Poole do not disclose and do not make these impurities, including their upper and lower limits, obvious .

24. Poole also states that "there is no maximum aluminum concentration label requirement for small volume parenterals" (Poole Page 2). As a scientist in the pharmaceutical art, selenium injection would be considered a small volume parenteral. Therefore, Poole supports my position discussed above that the label is different from the contents of the actual finished product and one or ordinary skill in the art would not know the aluminum content of Selepen or American Regent's old selenium product if it was not listed on the product label.

**American Regent Label**

25. In the Office Action, the Examiner refers to the American Regent Label for our new selenium 60 µg/mL product, which does indeed mention an aluminum content of not more than 2.5 µg/mL. However, the Examiner discusses that the product disclosed in our patent application is "identical" to our actual new and FDA approved finished product and that aluminum, chromium, and iron are known contaminants (Office Action at Page 5). I disagree with the Examiner that the American Regent Label is "identical" to the finished product. As discussed above, the label is not the product and cannot be "identical to it" although the label mentions the limits on the aluminum content that the product should have, the American Regent Label does not mention impurities such as chromium, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium and one of ordinary skill in the art would not know that these impurities can be from the selenium finished product and what those upper and lower impurity limits are. I do not know why the Examiner is assuming certain impurities are inherent in our new and FDA approved selenium products when none are listed on the American Regent Label, except for aluminum.

**Pluhator-Murton**

26. In the Office Action, the Examiner discusses that Pluhator-Murton teaches that PN solutions can comprise chromium and aluminum as contaminants (Office Action at Page 5) and that this reference makes our patent application obvious. I respectfully disagree with the Examiner. On reading Pluhator-Murton, this reference does not discuss or mention or list or test, among other contaminants or impurities, fluoride, silicon, potassium, magnesium, sodium and/or calcium in the selenium finished product. Moreover, there is no discussion as to what acceptable lower and upper limits of those impurities would be that are associated with the trace element

selenium.

27. More particularly, Pluhator-Murton discloses that there can be unintentional trace element contamination from components in parenteral nutrition (PN) (e.g., electrolytes, dextrose, amino acid, vitamins, etc.), where the PN is expected to be "free of trace elements" (see Pluhator-Murton at page 225). Pluhator-Murton illustrates this by scanning for 66 trace element contaminants or impurities in 8 PN samples. The trace element contaminants that were scanned are shown in Table I below.

TABLE I
*Trace elements measured with the "spectrum-directed" ICP-MS screen*

| | | | | | |
|---|---|---|---|---|---|
| Li (Lithium) | Ni (Nickel) | Zr (Zirconium) | Te (Tellurium) | Gd (Gadolinium) | Re (Rhenium) |
| Be (Beryllium) | Cu (Copper) | Nb (Niobium) | I (Iodine) | Tb (Terbium) | Os (Osmium) |
| B (Boron) | Zn (Zinc) | Mo (Molybdenum) | Xe (Xenon) | Dy (Dysprosium) | Ir (Iridium) |
| Al (Aluminum) | Ga (Gallium) | Ru (Ruthenium) | Cs (Cesium) | Ho (Holmium) | Pt (Platinum) |
| Sc (Scandium) | Ge (Germanium) | Rh (Rhodium) | Ba (Barium) | Er (Erbium) | Au (Gold) |
| Ti (Titanium) | As (Arsenic) | Pd (Palladium) | La (Lanthanum) | Tm (Thulium) | Hg (Mercury) |
| V (Vanadium) | Se (Selenium) | Ag (Silver) | Ce (Cerium) | Yb (Ytterbium) | Tl (Thallium) |
| Cr (Chromium) | Kr (Krypton) | Cd (Cadmium) | Pr (Praseodymium) | Lu (Lutetium) | Pb (Lead) |
| Mn (Manganese) | Rb (Rubidium) | In (Indium) | Nd (Neodymium) | Hf (Hafnium) | Bi (Bismuth) |
| Fe (Iron) | Sr (Strontium) | Sn (Tin) | Sm (Samarium) | Ta (Tantalum) | Th (Thorium) |
| Co (Cobalt) | Y (Yttrium) | Sb (Antimony) | Eu (Europium) | W (Tungsten) | U (Uranium) |

ICP-MS, inductively coupled plasma–mass spectrometry.

28. Of the 66 trace element contaminants scanned, 12 trace element contaminants were detected in 8 PN components (e.g., sodium chloride, amino acids, calcium gluconate, multivitamins, magnesium sulfate, potassium chloride, dextrose, and sterile water) where none were expected. The contaminants detected were Zn, Cu, Mn, Cr, Se, B, Al, Ti, Ba, V, As and Sr and their concentrations are shown in Figs. 1(a)-(h) (see Pluhator-Murton at pages 224 and 225 and Figs. 1(a)-(h)). Again, fluoride, silicon, potassium, magnesium, sodium and/or calcium were not scanned and therefore, not detected and none are associated with any intentionally added trace elements such as selenium.

29. Regarding intentionally added trace elements that have selenium, Pluhator-Murton tests the finished product MTE-6 (shown in Table III below), which has six trace elements: zinc 5 mg, copper 1 mg, manganese 0.5 mg, **chromium 10 µg,** selenium 60 µg, and **iodine 75 µg per 1 mL** for contaminants (emphasis added) and compares them to the actual MTE-6 label.

TABLE III
*Volume of components used to formulate a 1-L standard TPN solution*

| Solution | Volume (mL) |
|---|---|
| NaCl, 4 mM/mL | 11.66 |
| KCl, 2 mM | 22.22 |
| Travasol 10% without electrolytes | 300.00 |
| MTE-6 trace element concentrate* | 0.56 |
| Dextrose, 70% | 257.14 |
| Ca-gluconate, 10% | 19.16 |
| MVI adult multivitamin† | 5.56 |
| Mg-sulfate, 50% | 2.18 |
| Sterile water | 381.52 |
| Total | 1000.00 |

TPN, total parenteral nutrition.
*MTE-6 concentrate contains (per mL) Zn, 5 mg; Cu, 1 mg; Mn, 0.5 mg; Cr, 10 µg; Se, 60 µg; and I, 75 µg.
†MVI adult contains (per 10 mL) vitamin C, 1000 mg, vitamin A, 10,000 IU; vitamin D, 1000 IU; vitamin E, (*dl*-α-tocopheryl acetate), 10 IU; thiamine (as hydrochloride), 45 mg; riboflavin (as sodium phosphate), 10 mg; niacinamide, 100 mg; pyridoxine (as hydrochloride), 12 mg; *d*-pantothenic acid (as *d*-panthenol), 26 mg; and benzyl alcohol, 9 mg.

30. From Table III above as the red arrows indicate, MTE-6 has at least 10 times more chromium (10 µg/mL vs. less than 1 µg/mL) in it and at least 375 times more iodine (75 µg/mL vs. less than 0.125 µg/mL) in it compared to our new and FDA approved selenium products that have no or low impurity amounts of chromium and/or iodine. This is because chromium and iodine are added to the MTE-6 products as active ingredients and are not considered impurities by a scientist in the pharmaceutical arts.

31. Pluhator-Murton's results comparing the MTE-6 label to the actual MTE-6 product are shown in Table IV below.

TABLE IV
*Trace element amounts expected in a standard 2-L TPN solution, and the amount absorbed from a standard, oral diet calculated from a TPN solution composed of lot 1 components*

| Element | Expected amount in 2-L TPN solution (µg/2 L)* | Calculated amount that would be administered in 2-L TPN from lot 1 components (µg/2 L) | Reference average amount(s) absorbed from standard daily oral diet (µg) |
|---|---|---|---|
| Zn | 5560 | 6682 | 4000† |
| Cu | 1120 | 1202 | 640–840† |
| Mn | 560 | 598 | 165–200† |
| Cr‡ | 11 | 26 | 0.7–3.5† |
| Se | 67 | 88 | 80–160† |
| B | 0 | 1796 | 900–2700†§ |
| Al | 0 | 428 | 200†‖ |
| Ti | 0 | 10 | 2–20¶# |
| Ba | 0 | 72 | 36–54§** |
| V | 0 | 11 | 0.06–0.165† †† |
| As | 0 | 1 | 18–90† ‡‡ |
| Sr | 0 | 6 | 89–342§ |

TPN, total parenteral nutrition.
*Concentration of trace elements present in 1.2 mL MTE-6, based on American Medical Association daily IV trace element recommendations for TPN delivery: Zn, 2500–4000 µg/d; Cu, 500–1500 µg/d; Mn, 150–800 µg/d; Cr, 10–15 µg/d for stable adults.[18] Selenium is based on 40 to 120 µg/d.[18]

32. From Table IV indicated by the red arrow, the "expected amount" of selenium as well as the expected amount of zinc, copper, manganese, and chromium is above that indicated on the label (See also Pluhator-Murton at Page 222). Again, a scientist in the pharmaceutical art would understand that chromium and iodine are intentionally added to the MTE-6 product and would be considered active ingredients and not contaminants or impurities. Even if somehow they were considered contaminants or impurities, the chromium amount in the MTE-6 product is at least 10 times more (10 µg vs. less than 1 µg) and the iodine amount in the MTE-6 product is at least 375 times more per 1 mL (75 µg vs. less than 0.125 µg) compared to our new and FDA approved selenium 6 µg or 60 µg per 1 mL finished products.

33. Table IV of Pluhator-Murton also further exemplifies the understanding by scientists in the pharmaceutical art that the label is different from the contents of the actual finished product.

**Menendez**

34. In the Office Action, the Examiner discusses that Menendez mentions that iron is a known contaminant in PN (see Office Action at Page 5). On my review of Menendez, she tested dextrose, amino acids, lipids, potassium chloride, sodium chloride, magnesium sulfate, sodium glycerophosphate, sodium phosphate, calcium gluconate, zinc sulfate, and sterile water for iron contaminants. The results of her tests are shown below:

> **Results:** Iron levels for each individual solution were (µg/mL): mean value±SD: Dextrose 50%: 1.12±0.03; Dextrose 70%: 1.32±0.52; Amino acids 10%: 0.25±0,11; Lipids 20%: 4.58±0.80; Potassium chloride: 0.11±0.03; Sodium chloride 20%: 0.11±0,03; Magnesium sulfate: 0.11±0,00; Sodium glicerophosphate: 2.76±0.48; Sodium phosphate: 4.51±0.13; Calcium gluconate: 2,01±0,27; Zinc sulfate: 0.12±0,04; Sterile water: non detectable. According to the obtained values, the calculated iron total amount (mg) provided by the individual components contamination would be for a typical TPN mixture: adult 2.352; neonatology: 0.073; pediatric: 0.524. (Menendez Results, Full Summary-Exhibit G)

35. From Mendez's results, selenium was not added to the PN and therefore was not tested for iron contaminants. Of note, sterile water, which is what we use in our new and FDA approved selenium products had no detectable iron. Therefore, because selenium was not added to the PN and was not tested, Menendez does not recognize that selenium can be a source of iron impurities and what the lower limits or upper limits would be for the iron impurities associated with a selenium finished product.

36. Menendez also describes that iron contaminants can destabilize lipids in PN and concludes that "it would be advisable that manufacturers **declare the Fe contaminant content on the product label** to avoid iron excess which would compromise the evolution of critical patients". See Menendez Full Summary and emphasis added. Menedez, like the Poole and Pluhator-Murton references, also further exemplifies the understanding by scientists in the pharmaceutical art that the label is not "identical" to the actual finished product as mentioned by the Examiner.

37. In summary, I do not know why the Examiner is assuming certain impurities are inherent in our new and FDA approved 60 µg or 6 µg selenium per 1 mL products by combining the Selepen, Poole, American Regent Label, Pluhator-Murton and Menendez references together and saying that those impurities are in our new and FDA approved selenium products without those impurities (e.g., chromium, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium) and their upper and lower limits being described in those references.

**Our New Selenium Finished Products Meet a Long Felt and Persistent Need**

38. ASPEN is the American Society for Parenteral and Enteral Nutrition, which is a professional organization with members including dietitians, nurses, pharmacists, physicians and scientists who are involved in providing clinical nutrition to patients. ASPEN publishes position papers and special reports every so often.

39. In 2012, ASPEN published a position paper on recommended changes to available trace element products. See "A.S.P.E.N. position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products," Nutrition in Clinical Practice, Vol. 27, No. 4 (August 2012), pp. 440-491 (ASPEN 2012), which is already of record and attached as Exhibit B.

40. ASPEN 2012 identifies a need that the parenteral combination trace element products commercially available in the U.S. as of 2012 require "**significant modifications**" (see ASPEN 2012 Abstract) and that "**safer and more effective**" vitamin and trace element products are needed (see ASPEN 2012 at Page 455). Therefore, ASPEN 2012 identifies a long felt need for new trace element products and that those currently on the market in 2012 required "significant modifications."

41. The need for new and safer trace element products for parenteral nutrition was still unmet so much so that the FDA also had concerns about the currently available trace element products in 2012 and 2019 and warned manufacturers about unapproved drugs in 2019 (see FDA Warning Unapproved Drugs October 17, 2019 -Exhibit C). This long felt need persisted over 7 years until our selenium finished product was approved by the FDA and the selenium finished product was publicly made available on July 10, 2019 (Exhibit F). Our new selenium finished products containing 6 µg or 60 µg of selenium per 1 mL of the current claims satisfied this long felt need that ASPEN 2012 and the FDA identified.

42. Moreover, the new and FDA approved finished product containing 60 µg of selenium per 1 mL of, for example, claim 1 and the FDA approved selenium finished product containing 6 µg of selenium per 1 mL of, for example, also claim 1, were the first FDA approved selenium products that can safely and effectively supplement the trace element needs in a majority of patients. For example, due to the no or low fluoride and iodine impurities as well as other low impurities, the 6 µg of selenium per 1 mL finished product can be used in pediatric and neonatal patients that are less than 7 kilograms. Therefore, regarding for example, claim 1, we did more than routine optimization and satisfied this persistent and long felt need, which was not obvious.

**The New Selenium Trace Elements Finished Products Have Achieved Wide Spread Use and Commercial Success**

43. Our new and FDA approved selenium 60 µg and 6 µg selenium per 1 mL finished products of the current claims (e.g., claim 1) not only satisfied a long felt need for safe and effective selenium supplementation that persisted for years, but also achieved wide spread use and it is my understanding commercial success.

44. For adult and pediatric patients, our new and FDA approved selenium finished product containing 60 µg per 1 mL, now in, for example, claim 1, as discussed above would not be obvious. The concentration of 60 µg of selenium per 1 mL in an actual finished product as the sole active ingredient did not exist before our patent application and during manufacturing, particular attention was given to limit the amounts of chromium, aluminum, fluoride, silicon, potassium, magnesium, sodium and/or calcium in the finished selenium product as it could now be used safely and effectively in certain patient populations. The 60 µg of selenium per 1 mL finished product provides the clinician an easy and more accurate way of supplementing selenium by, often times, injecting a 1 mL dose of the composition for adults.

45. In the selenium finished product, we raised the concentration of selenium to 60 µg per 1 mL from the non-FDA approved 40 µg of selenium per 1 mL finished product of Selepen and American Regent's older selenium product. As stated above, increasing the concentration can lead to the introduction of higher concentrations of impurities and particular attention was given to limit the amounts of chromium, aluminum, fluoride, silicon, potassium, magnesium, sodium and/or calcium to make it suitable for use in adult and pediatric patients above 7 kilograms. Here the selenium concentration per 1 mL was increased while reducing or eliminating impurities in the 60 µg of selenium per 1 mL finished product.

46. Further, it was not only increasing the selenium to 60 µg per 1 mL in the finished product and limiting the introduction of impurities into the finished product, but we also had to improve the quality of raw materials used to make the finished product as we had to meet more stringent BET limits of NMT 50 EU/mL, in order for our new selenium finished product to be FDA approved. The unapproved older selenium 40 µg per 1 mL products did not have to meet such stringent BET requirements.

47. Our new and FDA approved selenium 60 µg per 1 mL finished product and connection to claim 1 of the current claims is shown in Table A below.

**Table A**

| **Active Ingredient per 1 mL FDA Approved Product Adult and Pediatric Patients** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 60 µg | Selenium about 60 µg |
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.3 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

48. For pediatric and neonatal patients, our new and FDA approved selenium finished product containing 6 µg per 1 mL of the current claims, now in, for example, claim 1, as stated above, would also not be obvious. The concentration of 6 µg of selenium per 1 mL did not exist before the current application and during manufacturing, particular attention was given to limit the amounts of chromium, aluminum, fluoride, silicon, potassium, magnesium, sodium and/or calcium to make it suitable for use in the neonatal population. The 6 µg of selenium per 1 mL finished product provides the clinician an easy and more accurate way of supplementing selenium by, often times, injecting a 1 mL dose of the composition as opposed to measuring a 0.1 mL dose of the more concentrated 60 µg of selenium for neonatal and/or pediatric patients of less than 7 kilograms. The larger volume allows less selenium to be lost in the IV tube set and IV bag especially when supplementing selenium in a neonatal patient. Moreover, our less concentrated 6 µg of selenium per 1 mL finished product reduces the risk that the neonatal patient will receive an overdose.

49. When we made the 6 µg per 1 mL selenium finished product, it involved not only reducing the concentration of selenium to 6 µg per 1 mL in the finished product and limiting the introduction of impurities into the finished product, but we also had to improve the quality of raw materials used to make the finished product. For example, we had to use more water during manufacturing and had to make sure the water had no or reduced impurities. Aluminum, chromium, fluoride and iodine can accumulate especially in, for example, neonatal patients, and we were very conscious of the particular upper limits of these impurities. We also had to meet more stringent BET limits of NMT 17.5 EU/mL, in order for our new selenium finished product to be FDA approved for use in pediatric and neonatal patients that had weights below 7 kilograms. The unapproved older selenium 40 µg per 1 mL products did not have to meet such stringent BET requirements and you would need 0.15 mL to have a dose of 6 µg, which was not easy for the clinician to draw up into a syringe and to accurately administer such a small volume.

50. Our new and FDA approved selenium 6 µg per 1 mL finished product and connection to claim 1 of the current claims is shown in Table B below.

**Table B**

| **Active Ingredient per 1 mL FDA Approved Product Pediatric And Neonatal Patients Less Than 7 Kilogram** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 6 µg | Selenium about 6 µg |
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.0045 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

51. Moreover, as stated above, both our selenium 60 µg/mL and 6 µg/mL finished products were the first FDA approved selenium products for safe and effective supplementation for a majority of adult, pediatric and/or neonatal patients. (See Exhibits D and E- American Regent FDA announcements).

52. In summary, our new and FDA approved selenium finished products at the specific concentrations and low impurities are new compositions and not mentioned in the references discussed by the Examiner. They are not the result of routine optimization, address a long felt commercial need, have wide spread use and post-filing commercial success and would not have been obvious to a person of ordinary skill in the art.

53. If our new and FDA approved selenium finished products at the specific concentrations of the current application were indeed so obvious or so routine, then why did someone else not make them and seek FDA approval before the current application was filed?

**Sale of American Regent's Selenium 60 µg/mL Finished Product**

54. I have been advised that the sale of American Regent's new and FDA approved selenium 60 µg/mL finished product can be used against the invention disclosed in our patent application. However, it cannot be used against the invention disclosed in our patent application if the sale of the actual selenium 60 µg/mL finished product was within 1 year of our patent application's filing date.

55. Because I am one of the inventors of this patent application and am an inventor of our selenium finished products, I am familiar when the actual finished product that we developed was on sale. Our selenium 60 µg/mL finished product that we developed containing no chromium, aluminum, fluoride, iron or low amounts of these impurities was on sale on July 10, 2019 (see Exhibit F), which is within one year of our patent application's filing date of July 2, 2020. This selenium 60 µg/mL finished product was based on the subject matter disclosed directly that I worked on with the other inventors Gopal Anyarambhatla and Jasmina Marinkovic.

56. The new and FDA approved selenium 6 µg/mL finished product (e.g., for neonatal use), was sold on March 31, 2022 (see Exhibit E), which is a date well after the date we filed our patent application.

57. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. All statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Richard P. Lawrence

12 DEC 2023

Date

**EXHIBIT A**

**RICHARD P. LAWRENCE**

| | |
|---|---|
| **JOB TITLE:** | Director, Technical Services |
| **QUALIFICATIONS:** | B.S. Chemistry/Mathematics<br>Fairleigh Dickinson University<br>Madison, New Jersey |
| **EXPERIENCE:** | |
| | **American Regent, Inc.**<br>(formerly Luitpold Pharmaceuticals, Inc.)<br>Shirley, New York |
| 07/2018 – Present | Director, Technical Services |
| 04/2003 – 07/2018 | Director, Research & Development |
| 09/2002 – 04/2003 | Director, Quality Assurance |
| 05/2002 – 09/2002 | Director, Quality Control |
| 03/1983 – 05/2002 | Manager, Product Development |
| | **Gibco Invenex**<br>Milburn, New Jersey |
| 10/1979 – 03/1983 | Research Chemist |

1848-32 US CON Track 1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | American Regent, Inc. | Examiner: | Ali Soroush |
| Serial No: | 18/124,391 | Art Unit: | 1617 |
| Filed: | March 21, 2023 | Conf. No.: | 3879 |
| For: | TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE | | |

December 13, 2023

**RESPONSE INCLUDING AMENDMENT**

This response is being submitted in reply to the Office Action mailed September 13, 2023. Accordingly, this response is filed timely on or before December 13, 2023.

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**CERTIFICATE OF EFS-WEB TRANSMISSION**

I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on December 13, 2023.

Date: December 13, 2023

/William D. Schmidt/
William D. Schmidt

**IN THE CLAIMS:**

1. (Currently Amended) An injectable composition comprising water, and about [[4]] 6 µg [[to]] or about [[90]] 60 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, [[and]] no iron or iron in an amount up to about 10 µg, and no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition.

2. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition comprises [[about]] 60 µg of selenium per 1 mL of the injectable composition.

3. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition comprises [[about]] 6 µg of selenium per 1 mL of the injectable composition.

4. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 0.0001 to about 0.6 mcg of aluminum per 1 mL of the injectable composition.

5. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 0.0001 to about 10 µg/mL of iron per 1 mL of the injectable composition.

6. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 0.0001 µg to about 2.7 µg of fluoride per 1 mL of the injectable composition ~~has a pH of about 1.0 to about 5~~.

7. (Cancelled).

8. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains no iodine or iodine in an amount up to about 0.2 ~~about 40~~ µg per 1 mL of ~~selenium~~ the injectable composition.

9. (Previously Presented) The injectable composition of claim 2, wherein the injectable composition has a pH of about 1.8 to about 2.4.

10. (Cancelled).

11. (Previously Presented) The injectable composition of claim 3, wherein the injectable composition has a pH of about 1.8 to about 2.4.

12. (Cancelled).

13. (Currently Amended) The injectable composition of claim 1, wherein the selenium is elemental selenium from selenious acid.

14. (Previously Presented) The injectable composition of claim 2, wherein the selenium is elemental selenium from selenious acid.

15. (Previously Presented) The injectable composition of claim 3, wherein the selenium is elemental selenium from selenious acid.

16. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition contains about 0.0001 µg/mL to about 0.25 µg/mL of chromium.

17. (Original) The injectable composition of claim 1, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum.

18. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains iodine in an amount of about 0.0001 µg ~~about 6~~ to about [[60]] 0.2 µg ~~of selenium~~ per 1 mL of the injectable composition.

19. (Currently Amended) The injectable composition of claim [[8]] 1, wherein ~~the selenium is elemental selenium from selenious acid~~ the injectable composition comprises about 0.0001 µg to about 0.25 µg of chromium; about 0.0001 µg to about 0.6 µg of aluminum; about 0.0001 µg to about 10 µg of iron; about 0.0001 µg to about 2.7 µg of fluoride; about 0.0001 µg to about 0.2 µg of iodine; and about 0.0001 µg to about 100 µg of silicon per mL of the injectable composition.

20.- 55. (Cancelled)

56. (Withdrawn) A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, about 4 µg to about 90 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, and no iron or iron in an amount up to about 10 µg per 1 mL of the injectable composition.

57.- 62. (Cancelled)

63. (Previously Presented) The injectable composition of claim 2, wherein the injectable composition is suitable for administration to an adult or pediatric patient.

64. (Cancelled).

65. (Previously Presented) The injectable composition of claim 3, wherein the injectable composition is suitable for administration to a pediatric or neonatal patient.

66. (Previously Presented) The injectable composition of claim 1, further comprising nitric acid.

67. (Currently Amended) The injectable composition of claim 2, further comprising nitric acid and the injectable composition has a bacterial endotoxin limit of not more than 50 EU/mL.

68. (Currently Amended) The injectable composition of claim 3, further comprising nitric acid and the injectable composition has a bacterial endotoxin limit of less than 17.50 EU/mL.

69. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition is in a volume that fills a 1 mL, 2 mL, 3 mL, 5 mL or 10 mL vial.

70. (Currently Amended) The injectable composition of claim [[8]] 3, ~~further comprising nitric acid~~ wherein the injectable composition comprises about 0.0001 µg to about 0.25 µg of chromium; about 0.0001 µg to about 0.6 µg of aluminum; about 0.0001 µg to about 10 µg of iron; about 0.0001 µg to about 2.7 µg of fluoride; about 0.0001 µg to about 0.2 µg of iodine; and about 0.0001 µg to about 100 µg of silicon per mL of the injectable composition.

71.-73. (Cancelled)

74. (Original) The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium.

75. (Previously Presented) The injectable composition of claim 1, wherein permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

76. (Currently Amended) An injectable composition consisting of water, nitric acid, selenious acid 98 µg as an active ingredient, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, [[and]] no iron or iron in an amount up to about 10 µg, and no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition.

77. (Currently Amended) An injectable composition consisting of water, nitric acid, selenious acid 9.8 µg as an active ingredient, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, [[and]] no iron or iron in an amount up to about 10 µg, and no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition.

78. (New) The injectable composition of claim 1, wherein the injectable composition is in a glass vial or ampule and has a silicon impurity in an amount of not more than 100 µg/mL.

79. (New) The injectable composition of claim 1, wherein the injectable composition has impurities of magnesium in an amount of not more than 15 µg, calcium in an amount of not more than 15 µg, sodium in an amount of not more than 7,200 µg and potassium in an amount of not more than 28,200 µg per 1 mL of the injectable composition.

## REMARKS

By this response, claim 1 has been amended to include the features of claims 2 and 3 that the composition comprises about 6 µg or about 60 µg of selenium per 1 mL of the injectable composition; and that the injectable composition contains no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition. Support for the amendments to claim 1 can be found throughout the specification, at least at paragraph [0087] and originally filed claims 2, 3, 4 and 63 of the specification. Claims 76 and 77 have been amended to include the feature that the injectable composition contains no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition (no fluoride or fluoride as an impurity). Support for the amendments to claims 76 and 77 can be found throughout the specification, at least at paragraph [0087] and originally filed claims 4 and 63 of the specification. Claim 8 has been amended to include the feature that the injectable composition contains no iodine or iodine in an amount up to about 0.2 µg per 1 mL of the injectable composition (no iodine or iodine as an impurity). Support for the amendments to claim 8 can be found throughout the specification, at least at paragraph [0087] and originally filed claims 4 and 63 of the specification. Claims 2-5 have been amended to keep them consistent with claim 1. Claims 6, 18, 19 and 70 have been amended to include the lower and upper limits of chromium, aluminum, iron, fluoride, iodine, and/or silicon as impurities. Support for the amendments to claims 6, 18, 19 and 70 can be found throughout the specification, at least at paragraph [0087] and originally filed claims 4, 5, 6 and 63 of the specification. Claims 67 and 68 have been amended to include that the injectable composition has a bacterial endotoxin limit of 50 EU/mL or 17.50 EU/mL. Support for claims 67 and 68 can be found, for example, in Tables 2 and 30. Claim 64 has been canceled without disclaimer and Applicant reserves the right to pursue this claim in one or more continuing applications.

New claim 78 has been added and includes that the impurity is silicon or silicon in an amount of not more than 100 µg/mL. Support for new claim 78 can be found, for example, in original claim 5 and Tables 2, 30, and 33. New claim 79 has been added and includes that the injectable composition has impurities of magnesium in an amount of not more than 15 µg, calcium in an amount of not more than 15 µg, sodium in an amount of not more than 7,200 µg and potassium in an amount of not more than 28,200 µg per 1 mL of the injectable composition. Support for new claim 79 can be found, for example, in original claims 5 and 75 and Tables 4 and 30.

The amendments do not add new matter. There are 30 claims pending in this application. Applicant respectfully requests entry of these amendments and allowance of the pending claims.

**1. Interview Summary**

In responding to the September 13, 2023 Office Action, Applicant's counsel, William D. Schmidt, conducted a telephone interview with Examiner Ali Soroush on October 24, 2023. Applicant thanks the Examiner for the time generously extended during the interview in which Applicant discussed proposed amendments to the claims of the current application. During the interview, the Examiner and Applicant's counsel discussed certain 35 U.S.C. §112, and §102/103 issues and proposed amendments to the claims. Applicant discussed that the cited references and the cited selenium product labels do not disclose chromium, iron, and fluoride as well as other trace element impurities that originate from the selenium finished product. Applicant discussed that just because impurities are not mentioned on the product labels does not mean that the finished selenium product does not have them. Applicant also discussed that the American Regent selenium 60 µg of selenium per 1 mL finished product does not qualify as prior art due to the exception of 35 U.S.C. §102(b)(1)(A) as the actual product was sold less than 1 year from Applicant's priority date. There was a discussion of providing one or more declarations of non-obviousness including secondary considerations. An agreement was not reached. Applicant has amended the claims and provides declarations consistent with the interview.

**2. Claim Rejections Under 35 U.S.C. §112**

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70 and 74-77 are rejected under 35 U.S.C. §112 as allegedly being indefinite for using the term "about" in the claims regarding the amount of selenium. Applicant respectfully disagrees and submits that the claims are clear to a person of ordinary skill in the art. For example, and not to be limiting, it is known in the pharmaceutical arts that the amount of the drug on the label is not an exact amount but will be within 90% to 110% of the amount indicated on the label as described in Tables 2 and 30 of the current specification.

Nevertheless, to advance the application without agreeing to the merits of the rejections, claim 1 has been amended to recite the specific amount of "about 6 µg or about 60 µg" of selenium

per 1 mL of the injectable composition, which is also clear to a person of ordinary skill in the art. Accordingly, the rejections under 35 U.S.C. §112 are moot.

**3. Claim Rejections Under 35 U.S.C. §102**

A. Claims 1, 6, 8, 13, 16, 18, 19, 66, 69, 70, 74 and 75 are rejected under 35 U.S.C. §102(a)(l) as allegedly being anticipated by Selenium IV Additive for use with TPN, Published 01/15/2008 (Selepen) as evidenced by Aluminum Exposure in Neonatal Patients Using the Least Contaminated Parenteral Nutrition Solution Products, Published 11/02/2012 (Poole). Applicant respectfully disagrees with the Office.

Regarding Item A (Selepen and Poole above), to advance the application without agreeing to the merits of the rejection, Applicant has amended claim 1 to include the features of claims 2 and 3 that the composition comprises about 6 µg of selenium or about 60 µg of selenium per 1 mL of the injectable composition. Because claims 2 or 3 are not part of the rejections based on Item A, Applicant submits that this aspect of the rejection is moot. See also Declaration of Richard Lawrence at Paragraphs 10, 37 and 45.

B. Claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, 74, 75 and 76 are rejected under 35 U.S.C. §102(a)(l) as allegedly being anticipated by Selenious Acid Injection, Published 04/2019 (American Regent Label) as evidenced by Trace Element Contamination of Total Parenteral Nutrition, Contribution of Component Solutions, Published 1999 (Pluhator-Murton-Exhibit H) and Iron contamination in parenteral nutrition mixtures, Published 11/14/2017 (Menendez-Exhibit G). Regarding Item B above, Applicant respectfully disagrees with the Office.

The Office contends that the American Regent Label teaches a sterile injectable solution of 60 µg selenium (as 98 µg selenious acid), water, and nitric acid having a pH of 1.8-2.4 that has an aluminum content of not more than 2.5 µg/mL (page 7, Description). The Office also contends that Pluhator-Murton teaches that total parenteral nutrition (PN) solutions can comprise chromium and aluminum as contaminants (abstract). The Office then uses the Menendez reference for teaching that iron is a known contaminant of total parenteral nutrition solution and can destabilize the lipids in them (abstract). Regarding the amounts of aluminum, chromium, and iron that are recited in the claims, the Office alleges that the composition of the American Regent Label is

"identical" to the instantly claimed composition and that aluminum, chromium, and iron are known as contaminants. Therefore, it would allegedly be expected that the composition of the American Regent Label inherently would comprise the same amounts of aluminum, chromium, and iron as contaminants as currently claimed (Office Action at Page 5).

Applicant has amended claims 1, 76 and 77 to include that the injectable composition contains no fluoride or fluoride in an amount up to about 2.7 µg per 1 mL of the injectable composition. Claims 6, 18, 19 and 70 have been amended, and new claim 79 has been added to include the lower and upper limits of chromium, aluminum, iron, fluoride, iodine, silicon, magnesium, calcium, sodium and/or potassium as impurities. Applicant submits that these claim features are not disclosed or made obvious by the American Regent Label, Pluhator-Murton and Menedez.

As an initial matter, the Office takes the position that the contaminants or impurities would be inherent properties in the cited references. Applicant respectfully disagrees with the Office's position as in order for the cited references to be used in a rejection as prior art, the prior art has to be enabling prior art. See, for example, *Impax Labs v. Aventis Pharmaceuticals* (Fed. Cir. 2008), where the court held that a proper prior art reference must be enabling for it to be used as prior art to anticipate the patent claims.

In the present case, the cited references do not enable a person of ordinary skill in the art to practice the claimed invention as the cited art does not disclose or make obvious that the selenium finished product can have, among other things, no chromium, no fluoride, no silicon, no magnesium, no calcium, no sodium, no potassium or impurity amounts of chromium, fluoride, silicon, magnesium, calcium, sodium, and/or potassium in the selenium finished product. Nor do these references disclose or make obvious what the lower and upper limits of these impurities would be in an FDA acceptable selenium finish product.

**A. The American Regent Label Does Not Anticipate or Make the Current Claims Obvious**

In the Office Action, the Office alleges that the composition in the American Regent Label is "identical to the instantly claimed composition and that aluminum, chromium, and iron are known as contaminants in the composition such as American Regent's composition" (Office

Action at Page 5). Applicant respectfully disagrees with the Office. Although the American Regent Label discloses selenium 60 µg/mL as the active ingredient, and also an aluminum content of not more than 2.5 µg/mL (Page 7, of the American Regent Label Description), there is no disclosure that chromium, iron, fluoride, iodine and/or silicon are impurities on that label.

Applicant emphasizes that the American Regent Label is not the finished selenium product and a person of ordinary skill in the art would understand that the American Regent Label is not "identical" to the finished product. This is particularly so as any impurities (e.g., chromium, iron, fluoride, iodine, silicon, potassium, magnesium, sodium and/or calcium) can enter the selenium finished product during manufacturer from, for example, the active selenium ingredient, excipients, stopper, vial, mixing vessels, filter, water, air, etc., which are all used during manufacture. The impurities are not listed on the label and their FDA acceptable lower or upper limits for that matter are likewise not listed on the label. See Declaration of Richard Lawrence at Paragraphs 19, and 24-37.

Further, the current claims are more than just testing for contaminants. The finished products obtained had no or very low levels of impurities that were difficult to detect, if at all, at the lower limits Applicant set. More particularly, during manufacturing of the new and FDA approved selenium finished products (e.g., 6 µg or 60 µg per 1 mL selenium finished products of claim 1), Applicant recognized that in addition to the selenious acid, the drug product manufacturing process, equipment and the container/closure components could also be a source of impurities. Applicant made sure, among other things, no chromium, iron, fluoride, iodine, sodium, potassium, magnesium, calcium and/or silicon or very low amounts of these impurities were not above Applicant's new established permitted daily limits (PDL) and Applicant's new control thresholds set for such impurities. These new selenium finished products were manufactured within Applicant's new control thresholds of less than 30% of the established PDL limits. See Declaration of Richard Lawrence at Tables C and D and Paragraphs 7-18. Further, Applicant respectfully requests that the Office provides a reference that shows Applicant's upper limits on chromium, iron, fluoride, iodine, sodium, potassium, magnesium, calcium and/or silicon and why these would be allegedly obvious. Accordingly, the claimed selenium finished products would not be obvious to a person of ordinary skill in the art. See Declaration of Richard Lawrence at Paragraphs 7-37. Therefore, Applicant submits that the American Regent Label and the selenium

60 µg per 1 mL finished product are not "identical" as asserted by the Office, and the American Regent Label as well as the other cited references do not disclose or make obvious the current claims.

Moreover, claims 6, 18, 19 and 70 have been amended, and new claim 79 has been added to include the lower and upper limits of chromium, aluminum, iron, fluoride, iodine, silicon, magnesium, calcium, sodium and/or potassium as impurities. For example, claims 19 and 70 include that the selenium contains about 0.0001 µg to about 0.25 µg of chromium; about 0.0001 µg to about 0.6 µg of aluminum; about 0.0001 µg to about 10 µg of iron; about 0.0001 µg to about 2.7 µg of fluoride; about 0.0001 µg to about 0.2 µg of iodine; and about 0.0001 µg to about 100 µg of silicon per mL of the injectable composition. None of the cited references disclose or make obvious that the selenium 60 µg finished product contains all 6 impurities per 1 mL at the claimed ranges recited in claims 19 and 70. Further, the claimed selenium finished products when administered to a patient would not exceed the permitted daily limits for impurities recited in claims 75 and 79.

**B. Pluhator-Murton Does Not Anticipate or Make the Current Claims Obvious**

The Office takes the position that Pluhator-Murton teaches that PN solutions can comprise chromium and aluminum as contaminants (Office Action at Page 5). Applicant respectfully disagrees with the Office's position and submits that on a fair and accurate reading of Pluhator-Murton, this reference does not anticipate or make obvious the pending claims as Pluhator-Murton does not contemplate, mention, list or test, among other contaminants or impurities, fluoride and silicon. Moreover, there is no discussion as to what an acceptable level of those impurities would be and that a finished selenium trace element product can be the source of those impurities or contaminants with or without it being added to parenteral nutrition.

More particularly, Pluhator-Murton discloses that there can be unintentional trace element contamination from components in parenteral nutrition (PN) (e.g., electrolytes, dextrose, amino acid, vitamins, etc.), where the PN is expected to be "free of trace elements" (see Pluhator-Murton at page 225). Pluhator-Murton illustrates this by scanning for 66 trace element contaminants[1] in 8 PN samples. The trace element contaminants that were scanned are shown in Table I below.

[1] Contaminants are not intentionally added to the PN.

TABLE I
*Trace elements measured with the "spectrum-directed" ICP-MS screen*

| | | | | | |
|---|---|---|---|---|---|
| Li (Lithium) | Ni (Nickel) | Zr (Zirconium) | Te (Tellurium) | Gd (Gadolinium) | Re (Rhenium) |
| Be (Beryllium) | Cu (Copper) | Nb (Niobium) | I (Iodine) | Tb (Terbium) | Os (Osmium) |
| B (Boron) | Zn (Zinc) | Mo (Molybdenum) | Xe (Xenon) | Dy (Dysprosium) | Ir (Iridium) |
| Al (Aluminum) | Ga (Gallium) | Ru (Ruthenium) | Cs (Cesium) | Ho (Holmium) | Pt (Platinum) |
| Sc (Scandium) | Ge (Germanium) | Rh (Rhodium) | Ba (Barium) | Er (Erbium) | Au (Gold) |
| Ti (Titanium) | As (Arsenic) | Pd (Palladium) | La (Lanthanum) | Tm (Thulium) | Hg (Mercury) |
| V (Vanadium) | Se (Selenium) | Ag (Silver) | Ce (Cerium) | Yb (Ytterbium) | Tl (Thallium) |
| Cr (Chromium) | Kr (Krypton) | Cd (Cadmium) | Pr (Praseodymium) | Lu (Lutetium) | Pb (Lead) |
| Mn (Manganese) | Rb (Rubidium) | In (Indium) | Nd (Neodymium) | Hf (Hafnium) | Bi (Bismuth) |
| Fe (Iron) | Sr (Strontium) | Sn (Tin) | Sm (Samarium) | Ta (Tantalum) | Th (Thorium) |
| Co (Cobalt) | Y (Yttrium) | Sb (Antimony) | Eu (Europium) | W (Tungsten) | U (Uranium) |

ICP-MS, inductively coupled plasma–mass spectrometry.

Of the 66 trace element contaminants scanned, 12 trace element contaminants were detected in 8 PN components (e.g., sodium chloride, amino acids, calcium gluconate, multivitamins, magnesium sulfate, potassium chloride, dextrose, and sterile water) where none were expected. The contaminants detected were Zn, Cu, Mn, Cr, Se, B, Al, Ti, Ba, V, As and Sr and their concentrations are shown in Figs. 1(a)-(g) (see Pluhator-Murton at pages 224 and 225 and Figs. 1(a)-(g)). Again, fluoride and silicon were not scanned and not detected.

Regarding intentionally added trace elements that have selenium, Pluhator-Murton tests the finished product MTE-6 (shown in Table III below), which has six trace elements: zinc 5 mg, copper 1 mg, manganese 0.5 mg, chromium 10 µg; selenium 60 µg, and iodine 75 µg per 1 mL for contaminants and compares it to the actual MTE-6 label.

TABLE III
*Volume of components used to formulate a 1-L standard TPN solution*

| Solution | Volume (mL) |
|---|---|
| NaCl, 4 mM/mL | 11.66 |
| KCl, 2 mM | 22.22 |
| Travasol 10% without electrolytes | 300.00 |
| MTE-6 trace element concentrate* | 0.56 |
| Dextrose, 70% | 257.14 |
| Ca-gluconate, 10% | 19.16 |
| MVI adult multivitamin† | 5.56 |
| Mg-sulfate, 50% | 2.18 |
| Sterile water | 381.52 |
| Total | 1000.00 |

TPN, total parenteral nutrition.
*MTE-6 concentrate contains (per mL) Zn, 5 mg; Cu, 1 mg; Mn, 0.5 mg; Cr, 10 µg; Se, 60 µg; and I, 75 µg.
†MVI adult contains (per 10 mL) vitamin C, 1000 mg; vitamin A, 10,000 IU; vitamin D, 1000 IU; vitamin E, (*dl*-α-tocopheryl acetate), 10 IU; thiamine (as hydrochloride), 45 mg; riboflavin (as sodium phosphate), 10 mg; niacinamide, 100 mg; pyridoxine (as hydrochloride), 12 mg; *d*-pantothenic acid (as *d*-panthenol), 26 mg; and benzyl alcohol, 9 mg.

As you can see from the red arrows in Table III, MTE-6 has at least 10 times more chromium in it (10 µg vs. 1 µg) and at least 375 times the amount of iodine in it (75 µg vs. 0.2 µg) compared to Applicant's selenium product of claim 1 and claim 8, respectively.

Pluhator-Murton's results comparing the MTE-6 label to the actual MTE-6 product are shown in Table IV below.

TABLE IV

*Trace element amounts expected in a standard 2-L TPN solution, and the amount absorbed from a standard, oral diet calculated from a TPN solution composed of lot 1 components*

| Element | Expected amount in 2-L TPN solution (µg/2 L)* | Calculated amount that would be administered in 2-L TPN from lot 1 components (µg/2 L) | Reference average amount(s) absorbed from standard daily oral diet (µg) |
|---|---|---|---|
| Zn | 5560 | 6682 | 4000† |
| Cu | 1120 | 1202 | 640–840† |
| Mn | 560 | 598 | 165–209† |
| Cr‡ | 11 | 26 | 0.7–3.5† |
| Se | 67 | 88 | 80–160† |
| B | 0 | 1796 | 900–2700†§ |
| Al | 0 | 428 | 200†¶ |
| Ti | 0 | 10 | 2–20¶# |
| Ba | 0 | 72 | 36–54§** |
| V | 0 | 11 | 0.06–0.165† †† |
| As | 0 | 1 | 18–90† ‡‡ |
| Sr | 0 | 6 | 89–342§ |

TPN, total parenteral nutrition.
*Concentration of trace elements present in 1.2 mL MTE-6, based on American Medical Association daily IV trace element recommendations for TPN delivery: Zn, 2500–4000 µg/d; Cu, 500–1500 µg/d; Mn, 150–800 µg/d; Cr, 10–15 µg/d for stable adults.[15] Selenium is based on 40 to 120 µg/d.[15]

As you can see from the red arrow, the expected amount of selenium as well as the expected amount of zinc, copper, manganese, and chromium is above that indicated on the label (See also Pluhator-Murton at Page 222). Applicant notes that chromium and iodine are intentionally added to the MTE-6 product and would not be considered contaminants or impurities by a person of ordinary skill in the art. See Declaration of Richard Lawrence at Paragraphs 26-33.

Even if they were considered contaminants or impurities, the chromium amount in the MTE-6 product is at least 10 times more and the iodine amount in the MTE-6 product is at least 375 times more per 1 mL compared to Applicant's selenium product of claim 1 and claim 8, respectively. Moreover, claims 76 and 77 use "consisting of" and exclude other active agents besides selenium. Therefore, it is not clear why a person of ordinary skill would use a reference like Pluhator-Murton that specifically teaches trace elements that use 10 times or more chromium and/or at least 375 times more iodine in it per 1 mL and assert that these are contaminants or impurities that allegedly

encompass the currently claimed selenium products. See Declaration of Richard Lawrence at Paragraphs 30-33.

Pluhator-Murton also further demonstrates Applicant's point that a label is not "identical" to the finished product as asserted by the Office. Either way, as stated above, Pluhator-Murton does not contemplate, mention, list or test, among other contaminants or impurities, fluoride and silicon.

**C. Menendez Does Not Anticipate or Make Obvious the Current Claims**

It is the Office's position that Menendez teaches iron as a known contaminant in PN (see Office Action at Page 5). Applicant respectfully submits that there are many components to PN as discussed above, and Menendez does not recognize or appreciate that contaminants or impurities can come from a selenium finished product.

More particularly, Menendez tested dextrose, amino acids, lipids, potassium chloride, sodium chloride, magnesium sulfate, sodium glycerophosphate, sodium phosphate, calcium gluconate, zinc sulfate, and sterile water for iron contaminants. Of note, sterile water had no detectable iron according to Menendez and selenium was not a component in Menendez's PN. Therefore, Menendez does not recognize that selenium can be a source of iron contamination and what the lower limits or upper limits would be for the iron contaminant associated with a selenium product. See Menendez Full Summary (Exhibit G).

Menendez also describes that iron contaminants can destabilize lipids in PN and concludes that "it would be advisable that manufacturers **declare the Fe contaminant content on the product label** to avoid iron excess which would compromise the evolution of critical patients". See Menendez Full Summary (Exhibit G) and emphasis added. Menedez also supports Applicant's position that the label is not "identical" to the actual finished product. Further, selenium is not mentioned, listed, tested or contemplated as being a source of an iron contaminant in Menendez's PN. See Declaration of Richard Lawrence at Paragraphs 34-37.

Claims 6, 18, 19 and 70 have been amended, and new claim 79 has been added to include the lower and upper limits of chromium, aluminum, iron, fluoride, iodine, silicon, magnesium, calcium, sodium and/or potassium as impurities in the selenium finished product. For example, none of the cited references disclose or make obvious that the selenium finished product contains

all 6 impurities (e.g., chromium, aluminum, iron, fluoride, iodine and silicon) per 1 mL at the claimed upper and lower limits recited in claims 19 and 70. Regarding claims 67 and 68, none of the cited references disclose or make obvious a selenium 60 µg or 6 µg per 1 mL finished product that contains no chromium, no aluminum, no iron, no fluoride or low amounts of chromium, aluminum, iron and/or fluoride as impurities, where the finished product has a bacterial endotoxin limit of 50 EU/mL or 17.50 EU/mL, which would now be acceptable by the FDA for a selenium product. See Declaration of Richard Lawrence at Paragraphs 16-18.

Therefore, withdrawal and reconsideration of the rejections of the claims under 35 U.S.C. §102 is respectfully requested.

**4. Claim Rejections Under 35 U.S.C. §103**

The Office rejects claims 3, 11, 15, 68 and 77 under 35 U.S.C. §103 as allegedly being obvious in view of the American Regent Label as evidenced by Pluhator-Murton and Menendez.

Applicant respectfully disagrees with the Office and refers the Office to the arguments above regarding the American Regent Label, Pluhator-Murton and Menendez and that these references do not disclose, among other impurities, chromium, iron, fluoride, iodine, and/or silicon and acceptable lower and upper limits for those impurities. Applicant submits that the currently claimed unique selenium finished products, are not obvious, met a long felt and persistent need, and have achieved wide spread use and commercial success.

**A. The New Selenium Finished Products Meet a Long Felt and Persistent Need**

Applicant submits that at least claims 1, 2 and 76 include the unique selenium finished product containing 60 µg of selenium per 1 mL that is a highly pure finished product, contains no chromium, no aluminum, no iron, no fluoride or low amounts of chromium, aluminum, iron and/or fluoride as impurities. This unique selenium finished product can be used, for example, in adult and pediatric patients.

Applicant also submits that at least claims 1, 3 and 77 include the unique selenium finished product containing 6 µg of selenium per 1 mL that is a highly pure finished product, contains no chromium, no aluminum, no iron, no fluoride or low amounts of chromium, aluminum, iron and/or fluoride as impurities. This unique selenium finished product can be used, for example, in

pediatric and neonatal patients.

The claimed unique selenium finished products of, for example, claim 1 met a long felt and persistent need that lasted over 7 years for the adult selenium finished product (60 µg of selenium per 1 mL) and over 10 years for the neonatal selenium finished product (e.g., 6 µg of selenium per 1 mL), without solution until the filing of the current application and are therefore not the result of routine optimization and would not have been obvious to a person of ordinary skill in the art.

To establish long felt need, Applicant must establish that (1) an art recognized need existed for a long period of time without solution; (2) the long felt need was not satisfied by another before the invention by the inventor; and (3) the invention satisfies that long-felt need. *Leo Pharmaceutical Products, Ltd. v. Rea,* 726 F. 3d 1346 (Fed. Cir. 2013) and MPEP 716.04.

Regarding the long felt need, items (1), (2) and (3) above, in 2012, ASPEN published a position paper on recommended changes that needed to be made to available trace element products. See "A.S.P.E.N. position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products," Nutrition in Clinical Practice, Vol. 27, No. 4 (August 2012), pp. 440-491 (ASPEN 2012), which is already of record and attached as Exhibit B.

ASPEN 2012 provides adult, pediatric and neonatal parenteral daily recommendations for trace elements. ASPEN 2012 identifies a need that the parenteral combination trace element products commercially available in the U.S. as of 2012 require "**significant modifications**" (see ASPEN 2012 Abstract) and that **"safer and more effective"** vitamin and trace element products are needed (see ASPEN 2012 at Page 455). Therefore, ASPEN 2012 identifies a long felt need for new trace element products and that those currently on the market in 2012 required "significant modifications."

The need for new and safer trace element products for parenteral nutrition was still unmet so much so that the FDA also had concerns about the currently available trace element products in 2012 and 2019 and warned manufacturers about unapproved drugs in 2019 (see FDA Warning Unapproved Drugs October 17, 2019 -Exhibit C). This long felt need persisted over 7 years until the selenium finished product was approved by the FDA and the selenium finished product was publicly made available in July 10, 2019 (Exhibit F). The new selenium finished product containing 6 µg or 60 µg of selenium per 1 mL of the current claims satisfied this long felt need

that ASPEN 2012 and the FDA identified.

Moreover, the unique selenium finished product containing 60 µg of selenium per 1 mL of, for example, claims 1, 2 and 76 and the unique selenium finished product containing 6 µg of selenium per 1 mL of, for example, claims 1, 3 and 77 were the first FDA approved selenium products that can safely and effectively supplement the trace element needs in a majority of patients. For example, due to the no or low fluoride and iodine impurities as well as other impurities, the 6 µg of selenium per 1 mL finished product can be used in pediatric and neonatal patients. Therefore, regarding for example, claim 1, Applicant did more than routine optimization. They satisfied this persistent and long felt need, and it was not obvious. See Declaration of Richard Lawrence at Paragraphs 28-42.

**B. The New Trace Elements Finished Products Have Achieved Wide Spread Use and Commercial Success**

Applicant submits that these unique selenium finished products of the current claims (e.g., claim 1, 2 and 3) not only satisfied a long felt need for safe and effective selenium supplementation that persisted for years in the art, but also achieved wide spread use and commercial success. See Declaration of Richard Lawrence at Paragraphs 43-53 and Declaration of Ms. Joann Gioia at Paragraphs 4-12.

In order to establish commercial success, the patentee must establish that a connection (or nexus) exists between the novel aspects of the patent claim(s) and the alleged commercial success. Where the claimed invention is a unique combination of known elements from the prior art…sales figures alone are also evidence of commercial success. See *Chemours Co. FC, LLC v. Daikin Indus., Ltd.,* 4 F.4th 1378 (Fed. Cir. 2021) and MPEP 716.03(b).

Applicant submits that the unique selenium finished product containing 60 µg of selenium per 1 mL for use in adult and pediatric patients and 6 µg of selenium per 1 mL finished product for use in pediatric and neonatal patients of the current claims led to their commercial success and satisfied a long felt need for safe and effective selenium supplementation.

For adult and pediatric patients, the unique selenium finished product containing 60 µg per 1 mL of the current claims, now in, for example, claim 1, would not be obvious. The concentration of 60 µg of selenium per 1 mL in an actual finished product as the sole active

ingredient did not exist before the current application and particular attention was given to limit the amounts of chromium, aluminum, fluoride and other impurities in the finished selenium product as it could now be used safely and effectively in certain patient populations. The 60 µg of selenium per 1 mL finished product provides the clinician an easy and more accurate way of supplementing selenium by, often times, injecting a 1 mL dose of the composition for adults. More particularly, the concentration of selenium was raised to 60 µg of selenium per 1 mL from the non-FDA approved 40 µg of selenium per 1 mL finished product of Selepen and other manufacturers.

Increasing the concentration can lead to the introduction of higher concentrations of impurities and thus particular attention was given to limit the amounts of chromium, aluminum, fluoride and other impurities in this patient specific population. As a result, the selenium concentration per 1 mL was increased while reducing or eliminating impurities in the 60 µg of selenium per 1 mL finished product. See Declaration of Richard Lawrence at Paragraphs 11, and 45-46.

Applicant clearly establishes the connection or nexus between the 60 µg of selenium per 1 mL with that of claim 1 of the current claims as shown in Table A below.

**Table A**

| **Active Ingredient per 1 mL FDA Approved Product Adult and Pediatric Patients** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 60 µg | Selenium about 60 µg |
| | |
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.3 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

For pediatric and neonatal patients, the unique selenium finished product containing 6 µg per 1 mL of the current claims, now in, for example, claim 1, would also not be obvious. The concentration of 6 µg of selenium per 1 mL did not exist before the current application and particular attention was given to limit the amounts of chromium, aluminum, fluoride, iodine and other impurities in the neonatal population. The 6 µg of selenium per 1 mL finished product provides the clinician an easy and more accurate way of supplementing selenium by, often times, injecting a 1 mL dose of the composition as opposed to measuring a 0.1 mL dose of the more concentrated 60 µg of selenium for neonatal and/or pediatric patients. The larger volume allows less selenium to be lost in the IV tube set and IV bag especially when supplementing selenium in a neonatal patient. See Declaration of Richard Lawrence at Paragraphs 13 and 48.

Applicant clearly establishes the connection or nexus between the 6 µg of selenium per 1 mL selenium finished products and the current claims in Table B below.

**Table B**

| **Active Ingredient per 1 mL FDA Approved Product Pediatric And Neonatal Patients Less Than 7 Kilograms** | **(Serial No. 18/124,391) Claim 1 Active Ingredient per 1 mL** |
|---|---|
| Selenium 6 µg | Selenium about 6 µg |

| | |
|---|---|
| **Elemental Impurity per 1 mL FDA Approved Product** | **Elemental Impurity of Claim 1 per 1 mL** |
| Chromium <0.0045 µg | No chromium or chromium not to exceed 1 µg |
| Aluminum <0.75 µg | No aluminum or aluminum not to exceed 6 µg |
| Iron <3 µg | No iron or iron up to about 10 µg |
| Fluoride <0.125 µg | No fluoride or fluoride up to about 2.7 µg |

Moreover, as stated above, both selenium 60 µg/mL and 6 µg/mL were the first FDA approved selenium products for safe and effective supplementation for a majority of adult, pediatric and/or neonatal patients. (See Exhibits D and E- American Regent FDA announcements). See Declaration of Ms. Joann Gioia at Paragraphs 4-8.

While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. See, for example, *Leo Pharms., Inc. v. Rea*, 726 F.3d at 1358. (Fed. Cir. 2013).

Applicant submits that the unique selenium 60 µg/mL and 6 µg/mL finished products with low or no impurities of the current claims led to their post-FDA filing commercial success as evidenced by the yearly gross sales connected with, for example, claim 1.

For example, the selenium 60 µg/mL product was launched on July 10, 2019 (Exhibit F) and had over $39 million in direct sales in 2019. In 2020, the direct sales of the selenium 60 µg/mL product increased to over $93 million and in 2021, the direct sales continued to increase to over $111 million. In 2022, the direct sales were lower at $87 million but this was largely due to the availability of the selenium 6 µg/mL product (e.g., for neonatal use).

Regarding the selenium 6 µg/mL product (e.g., for neonatal use), it launched on March 31, 2022 (Exhibit E) and had over $200 million in direct sales for 2022. Moreover, the commercial success was not due to any significant marketing effort by American Regent. See Declaration of Ms. Joann Gioia at Paragraphs 9-12.

In summary, Applicant's unique selenium products at the specific concentrations are new compositions not known in the cited art. They are not the result of routine optimization, address a long felt commercial need, have wide spread use and post-filing commercial success, and would

not have been obvious to a person of ordinary skill in the art. See Declaration of Richard Lawrence at Paragraphs 7-18, and 43-53.

Furthermore, Applicant respectfully submits that based on the references cited by the Office, it appears that the Office is using improper hindsight reconstruction in the rejections. To that end, Applicant cautions the Office against the use of hindsight reconstruction. In the CAFC case of *Mintz v. Dietz & Watson, Inc*., 679 F.3d 1372 (Fed. Cir. 2012) "hindsight" is mentioned repeatedly in the case, and the court warned against "the forbidden use of hindsight" and the "prohibited reliance on hindsight," as well as the need for "a court to walk a tightrope blindfolded (to avoid hindsight)." Additionally, MPEP 2142, states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." As such, given that there is nothing in the art that would motivate one of ordinary skill in the art to combine those references in the manner suggested by the Office, it is apparent that the rejection is based on improper hindsight recreation of the claims using the teachings of the present application as a road map.

Therefore, withdrawal and reconsideration of the rejections of claims under 35 U.S.C. § 103(a) is respectfully requested.

**C. Sale of American Regent's Selenium 60 µg/mL Finished Product Does Not Qualify as Prior Art**

Should the Office consider raising the sale of American Regent's selenium 60 µg/mL finished product as prior art to the current claims, Applicant respectfully submits that American Regent's selenium 60 µg/mL finished product containing no chromium, aluminum, fluoride, iron or low amounts of these impurities was on sale on July 10, 2019 (see Exhibit F), which is within one year of Applicant's July 2, 2020 priority date of the current application. This selenium 60 µg/mL finished product was based on the subject matter disclosed directly based on the work of the inventors Richard Lawrence, Gopal Anyarambhatla, and Jasmina Marinkovic. See Declaration of Richard Lawrence at Paragraphs 54-56. Accordingly, American Regent's selenium 60 µg/mL finished product falls under the 1 year grace period due to the exception of 35 U.S.C. §102(b)(1)(A).

Additionally, regarding the selenium 6 µg/mL product (e.g., for neonatal use), it launched on March 31, 2022, which is well after Applicant's July 2, 2020 priority date of the current application and the sale is clearly not prior art.

**5. No Disclaimers or Disavowals**

Although the present communication may include alterations to the claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited reference. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history may not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

**6. Conclusion**

No fee is believed to be due with respect to filing this response. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 50-5960 for such sum.

If the Office has any questions regarding the present application, the Office is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,

/William D. Schmidt/
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| SOROUSH, ALI | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ctrentacoste@slsllp.com
mtorres@slsllp.com
wschmidt@slsllp.com

# Office Action Summary

| Application No. | Applicant(s) | | |
|---|---|---|---|
| 18/124,391 | Anyarambhatla et al. | | |
| **Examiner** | **Art Unit** | **AIA (FITF) Status** | |
| ALI SOROUSH | 1617 | Yes | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 12/13/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1-6,8-9,11,13-19,56,63,65-70 and 74-79 is/are pending in the application.

5a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-6,8-9,11,13-19,63,65-70 and 74-79 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 12132023.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Continuation of Disposition of Claims* 5a) Of the above claim(s) is/are withdrawn from consideration: 56

## DETAILED ACTION

### *Notice of Pre-AIA or AIA Status*

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

### *Acknowledgement of Receipt*

Applicant's response filed on 12/13/2023 to the Office Action mailed on 09/13/2023 is acknowledged.

### *Claim Status*

Claims 1-6, 8, 9, 11, 13-19, 56, 63, 65-70, and 74-79 are pending.

Claims 7, 10, 12, 20-55, 57-62, and 71-73 were previously cancelled and claim 64 is cancelled.

Claim 56 is withdrawn as being directed to a non-elected invention.

Claims 1-6, 8, 13, 18, 19, 67, 68, 70, 76, and 77 are currently amended.

Claims 78 and 79 are newly added.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 have been examined.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 are rejected.

### *Priority*

Priority to CON 17/365,695 filed on 07/01/2012, which claims priority to application 63/047,708 filed on 07/02/2020.

***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on 12/13/2023 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

***Maintained Claim Rejections - 35 USC § 112***

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

This rejection was reiterated from the previous Office Action and modified in view of the amendments to the claims

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

The term “about” in claims 1-6, 8, 9, 11, 16-18, and 74-77 is a relative term which renders the claim indefinite. The term “about” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 2, 3, 13, 14, 15, 19, 63, 65-70, 78 and 79 are rejected for being dependent directly or indirectly claim 1 which is indefinite and includes all the limitations thereof.

***Response to Applicant's Arguments***

Applicant argues that the claims have been amended to recite about 6µg or 60µg of selenium and that the term "about" is well known in the pharmaceutical arts is not an exact amount but will be within 90% to 110% of the amount indicated. Applicant's argument has been fully considered but found not to be persuasive. Applicant has not provided any evidence beyond arguments that one of ordinary skill in the art would understand that about is within 90% to 110% of the amount indicated. Furthermore, the fact that this amount is not necessarily in the range Applicant argued is proven by Applicant's own argument. Applicant's argument explicitly states "For example, **and not to be limiting**, it is known in the pharmaceutical arts". The fact that the term "about" does not have any metes and bounds that can be clearly ascertained renders it indefinite. For the same reasons new claims 78 and 79 are rejected.

***Withdrawn, Maintained, and New Claim Rejections - 35 USC § 102***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

This rejection is reiterated from the previous Office Action and modified in view of the amendments to the claims.

Claim(s) 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, and 74-79 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017).

American Regent with regard to claim 1 teach a sterile injectable solution consisting of 60 µg selenium (as 98µg selenious acid), water, and nitric acid having a pH of 1.8-2.4 in a 10ml vial and has an aluminum content of not more than 2.5µg/ml (page 7, Description). Pluhator-Murton et al. teach that total parenteral nutrition solutions comprise chromium and aluminum as contaminants (abstract). Menendez et al. teach iron is a known contaminant of total parenteral nutrition solution (abstract). With regard to the amounts of aluminum, chromium, and iron, the Examiner notes that the composition of American Regent is identical to the instantly claimed composition and that aluminum, chromium, and iron are known as contaminants in the compositions such as the American Regent composition. Therefore, it would be expected that the composition of American Regent inherently comprises the same amounts of aluminum, chromium, and iron as contaminants. For the foregoing reasons the instant claims are anticipated by the prior art.

***Response to Applicant's Arguments and Affidavits on Filed on 12/13/2023***

The rejection of claims 1, 6, 8, 13, 16, 18, 19, 66, 69, 70, 74, and 75 under 35 U.S.C. 102(a)(1) as being anticipated by Selepen (Selenium IV Additive for use with TPN, Published 01/15/2008) as evidenced by Poole et al. (Aluminum Exposure in Neonatal Patients Using the Least Contaminated Parenteral Nutrition Solution Products, Published 11/02/2012) is withdrawn in view of the amendments to the claims.

With regard to the rejection of claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, and 74-79 under 35 U.S.C. 102(a)(1) as being anticipated by American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017):

Applicant argues that the instantly claimed amount of impurities and their amounts would not be inherent to the composition of American Regent since the composition of American Regent composition is not the finished product and the contaminants can be introduced when making the finished product. Applicant's argument has been fully considered but found not to be persuasive. Applicant's argument rests on the fact that the impurities instantly claimed are not explicitly disclosed by American Regent. First, Applicant has not shown with evidence that the product of American Regent is not a finished product. The assertion is merely attorney's argument. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from

common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). Furthermore, the argument is based on what may or is likely to occur but not on what the actual properties of the composition of American Regent actually consists of. Applicant has not shown through evidence that the product of American Regent includes even one of the claimed impurities in an amount that is outside of the instantly claimed range. Impurities in formulations are the inherent result of the manufacturing process and ingredients used. Applicant has not provided any evidence that there is any distinction between the claimed method of making and the method of making in American Regent. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the relevant time, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Therefore, the fact that instantly claimed contaminants and the amounts of such contaminants are not explicitly disclosed is insufficient not evidence that the amounts are not inherent to the composition of American Regent.

With regard to the Applicant's arguments that Pluhator-Murton et al. and Menendez et al. do not anticipate the instant claims, it should be noted that these references are only relied on for evidentiary purposes of showing it was already well known in the art that alumnium, iron, and chromium are known contaminants in trace element compositions. Therefore, Applicant's arguments with regard to these references are moot as they are not the basis for any rejections in the office action.

Finally, with regard to Applicant's argument of secondary consideration, in the Affidavit filed on 12/13/2023 by Joann Gioia, the arguments are not persuasive. Evidence of secondary

considerations, such as unexpected results or commercial success, is irrelevant to 35 U.S.C. 102 rejections and thus cannot overcome a rejection so based. In re Wiggins, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973).

For the foregoing reasons the rejection is maintained and new claims 78 and 79 are rejected.

***Maintained Claim Rejections - 35 USC § 103***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

This rejection is reiterated from the previous Office Action and modified in view of the amendments to the claims.

Claim(s) 3, 11, 15, 68, and 77 is/are rejected under 35 U.S.C. 103 as being unpatentable over American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017), as applied to claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, and 74-79 above.

The teachings of American Regent, Pluhator-Murton et al., and Menendez et al. are discussed above.

American Regent does not expressly teach a composition comprising 6µg/ml selenium and/or 9.8µg/ml of selenious acid. However, American Regent renders such a composition obvious.

It would have been prima facie obvious to one of ordinary skill in the art at the time of effective filing date of the instant invention to dilute the composition of American Regent to arrive at the instant amount and have a reasonable expectation of success. One would have been motivated to do so through routine optimization of the composition for a particular patient in view of their age, gender, and/or weight. For the foregoing reasons the instant claims are rendered obvious by the teachings of the prior art.

***Response to Applicant's Arguments and Affidavits on Filed on 12/13/2023***

Applicant argues that the instant claims are not rendered obvious by the teachings of the prior art as they have proven a long-felt need and commercial success. Applicant's argument has been fully considered but found not to be persuasive. The difference between the instant claims and the prior art claims is the amount of selenium in the composition. Therefore, the secondary evidence must show that reason for commercial success or the long-felt need is the result of the amount of selenium. Applicant makes no such connection. For the foregoing reasons the rejection is maintained.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for

more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/124,391 | 03/21/2023 | Gopal Anyarambhatla | 1848-32-CON-TRK1 | 3879 |

109802 7590 02/28/2024

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| EXAMINER |
|---|
| SOROUSH, ALI |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/28/2024 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ctrentacoste@slsllp.com
mtorres@slsllp.com
wschmidt@slsllp.com

| Applicant-Initiated Interview Summary | Application No. 18/124,391 | Applicant(s) Anyarambhatla et al. | | |
|---|---|---|---|---|
| | Examiner ALI SOROUSH | Art Unit 1617 | AIA (First Inventor to File) Status Yes | Page 1 of 1 |

| All Participants (applicant, applicants representative, PTO personnel) | Title | Type |
|---|---|---|
| ALI SOROUSH | Primary Examiner | Telephonic |
| William D. Schmidt | Attorney of Record | |

**Date of Interview:** 22 February 2024

**Issues Discussed:**

**35 U.S.C. 112**

The Applicant has suggested amending all the claims reciting "about" to delete the word. The Examiner agreed to that this amendment would be sufficient to overcome the rejection.

**35 U.S.C. 102**

Applicant argues the rejection of claims 1, 2,4, 6, 9, 13, 14, 16, 17, 18, , 63, 66, 67, 69 and 74-79 under 35 U.S.C. 102(a)(1) as being anticipated by American Regent as evidenced by Pluhator-Murton et al. and Menendez et al.does not teach the limitations of claims 6 and 18. The Examiner agreed that if the limitations of claims 6 and/or 18 are written in independent form it would be sufficient to overcome the rejections of record.

| /ALI SOROUSH/<br>Primary Examiner, Art Unit 1617 | |
|---|---|

**Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04**
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

**Applicant recordation instructions:** The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

**Examiner recordation instructions:** Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

1848-32 US CON Track 1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | American Regent, Inc. | Examiner: | Ali Soroush |
| Serial No: | 18/124,391 | Art Unit: | 1617 |
| Filed: | March 21, 2023 | Conf. No.: | 3879 |
| For: | TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE | | |

March 1, 2024

**RESPONSE INCLUDING AMENDMENT**

This response is being submitted in reply to the Final Office Action mailed February 1, 2024. Accordingly, this response is filed timely today. Applicant requests that this response be considered under the After Final Consideration Pilot Program 2.0.

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**CERTIFICATE OF EFS-WEB TRANSMISSION**

I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on March 1, 2024.

Date: March 1, 2024

/William D. Schmidt/
William D. Schmidt

**IN THE CLAIMS:**

1. (Currently Amended) An injectable composition comprising water, ~~and about~~ 6 µg or ~~about~~ 60 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, no iron or iron in an amount up to ~~about~~ 10 µg, and ~~no fluoride or~~ fluoride in an amount of 0.0001 µg [[up]] to ~~about~~ 2.7 µg per 1 mL of the injectable composition.

2. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition comprises 60 µg of selenium per 1 mL of the injectable composition.

3. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition comprises 6 µg of selenium per 1 mL of the injectable composition.

4. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~about~~ 0.0001 µg to ~~about~~ 0.6 ~~mcg~~ µg of aluminum per 1 mL of the injectable composition.

5. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~about~~ 0.0001 µg to ~~about 10 µg/mL~~ 10 µg of iron per 1 mL of the injectable composition.

6. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition ~~contains about 0.0001 µg to about 2.7 µg of fluoride per 1 mL of the injectable composition~~ is suitable for administration to an adult or pediatric patient when added to parenteral nutrition.

7. (Cancelled).

8. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~no iodine or~~ iodine in an amount [[up]] of 0.0001 µg to ~~about~~ 0.2 µg per 1 mL of the injectable composition.

9. (Currently Amended) The injectable composition of claim [[2]] 1, wherein the injectable composition has a pH of ~~about~~ 1.8 to ~~about~~ 2.4.

10. (Cancelled).

11. (Currently Amended) The injectable composition of claim [[3]] 1, wherein the injectable composition further comprises nitric acid ~~has a pH of about 1.8 to about 2.4~~.

12. (Cancelled).

13. (Previously Presented) The injectable composition of claim 1, wherein the selenium is elemental selenium from selenious acid.

14. (Previously Presented) The injectable composition of claim 2, wherein the selenium is elemental selenium from selenious acid.

15. (Previously Presented) The injectable composition of claim 3, wherein the selenium is elemental selenium from selenious acid.

16. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~about~~ 0.0001 µg/mL to ~~about~~ 0.25 µg/mL of chromium.

17. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains ~~about~~ 1 ppm to ~~about~~ 6 µg/mL of aluminum.

18. (Currently Amended) [[The]] An injectable composition ~~of claim 1~~ comprising water, 6 µg or 60 µg of selenium, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, no iron or iron in an amount up to 10 µg, and ~~wherein the injectable composition contains~~ iodine in an amount of ~~about~~ 0.0001 µg to ~~about~~ 0.2 µg per 1 mL of the injectable composition.

19. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition comprises ~~about~~ 0.0001 µg to ~~about~~ 0.25 µg of chromium; ~~about~~ 0.0001 µg to ~~about~~ 0.6 µg of aluminum; ~~about~~ 0.0001 µg to ~~about~~ 10 µg of iron; ~~about 0.0001 µg to about 2.7 µg of fluoride; about~~ 0.0001 µg to ~~about~~ 0.2 µg of iodine; and ~~about~~ 0.0001 µg to ~~about~~ 100 µg of silicon per mL of the injectable composition.

20.- 55. (Cancelled)

56. (Cancelled)

57.- 62. (Cancelled)

63. (Currently Amended) The injectable composition of claim [[2]] 18, wherein the injectable composition is suitable for administration to an adult or pediatric patient.

64. (Cancelled).

65. (Currently Amended) The injectable composition of claim 3, wherein the injectable composition is suitable for administration to a pediatric or neonatal patient when added to parenteral nutrition.

66. (Currently Amended) The injectable composition of claim [[1]] 18, ~~further comprising nitric acid~~ wherein the selenium is elemental selenium from selenious acid.

67. (Currently Amended) The injectable composition of claim [[2]] 18, wherein the injectable composition comprises 60 µg of selenium per 1 mL of the injectable composition ~~further comprising nitric acid and the injectable composition has a bacterial endotoxin limit of not more than 50 EU/mL~~.

68. (Currently Amended) The injectable composition of claim [[3]] 18, wherein the injectable composition comprises 6 µg of selenium per 1 mL of the injectable composition ~~further comprising nitric acid and the injectable composition has a bacterial endotoxin limit of less than 17.50 EU/mL~~.

69. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition is in a volume that fills a 1 mL, 2 mL, 3 mL, 5 mL or 10 mL vial.

70. (Currently Amended) The injectable composition of claim [[3]] 18, wherein the injectable composition comprises ~~about~~ 0.0001 µg to ~~about~~ 0.25 µg of chromium; ~~about~~ 0.0001 µg to ~~about~~ 0.6 µg of aluminum; ~~about~~ 0.0001 µg to ~~about~~ 10 µg of iron; ~~about~~ 0.0001 µg to ~~about~~ 2.7 µg of fluoride; ~~about 0.0001 µg to about 0.2 µg of iodine;~~ and ~~about~~ 0.0001 µg to ~~about~~ 100 µg of silicon per mL of the injectable composition.

71.-73. (Cancelled)

74. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains less than ~~about~~ 0.25 µg/mL of chromium.

75. (Currently Amended) The injectable composition of claim 1, wherein permitted daily limits (PDL) of the injectable composition do not exceed ~~about~~ 0.4 µg/ day of cadmium, ~~about~~ 0.5 µg/ day of lead, ~~about~~ 1.5 µg/ day of arsenic, ~~about~~ 0.4 µg/ day of mercury, ~~about~~ 1 µg/ day of cobalt, ~~about~~ 2 µg/ day of vanadium, ~~about~~ 4 µg/ day of nickel, ~~about~~ 1.6 µg/ day of thallium, ~~about~~ 20 µg/ day of gold, ~~about~~ 2 µg/ day of palladium, ~~about~~ 2 µg/ day of iridium, ~~about~~ 2 µg/ day of osmium, ~~about~~ 2 µg/ day of rhodium, ~~about~~ 2 µg/ day of ruthenium, ~~about~~ 2 µg/ day of silver, ~~about~~ 2 µg/ day of platinum, ~~about~~ 50 µg/ day of lithium, ~~about~~ 18 µg/ day of antimony, ~~about~~ 140 µg/ day of barium,

~~about~~ 300 µg/ day of molybdenum, ~~about~~ 120 µg/ day of tin, ~~about~~ 1 µg/ day of chromium, ~~about~~ 6 µg/ day of aluminum, ~~about~~ 50 µg/ day of boron, ~~about~~ 50 µg/ day of calcium, ~~about~~ 10 µg/ day of iron, ~~about~~ 94,000 µg/ day of potassium, ~~about~~ 50 µg/ day of magnesium, ~~about~~ 24,000 µg/ day of sodium, ~~about~~ 1 µg/ day of tungsten, and/or ~~about~~ 100 µg/ day of silicon.

76. (Currently Amended) An injectable composition consisting essentially of water, nitric acid, selenious acid 98 µg ~~as an active ingredient~~, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, no iron or iron in an amount up to ~~about~~ 10 µg, and ~~no fluoride or~~ fluoride in an amount of 0.0001 µg [[up]] to ~~about~~ 2.7 µg or iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable composition.

77. (Currently Amended) An injectable composition consisting essentially of water, nitric acid, selenious acid 9.8 µg ~~as an active ingredient~~, no chromium or chromium in an amount not to exceed 1 µg, no aluminum or aluminum in an amount not to exceed 6 µg, no iron or iron in an amount up to ~~about~~ 10 µg, and ~~no fluoride or~~ fluoride in an amount of 0.0001 µg [[up]] to ~~about~~ 2.7 µg or iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable composition.

78. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition is in a glass vial or ampule and has a silicon impurity in an amount of not more than 100 µg/mL.

79. (Currently Amended) The injectable composition of claim [[1]] 18, wherein the injectable composition further comprises nitric acid and has a pH of 1.8 to 2.4 ~~has impurities of magnesium in an amount of not more than 15 µg, calcium in an amount of not more than 15 µg, sodium in an amount of not more than 7,200 µg and potassium in an amount of not more than 28,200 µg per 1 mL of the injectable composition~~.

## REMARKS

By this response, independent claim 1 has been amended consistent with the February 22, 2024 interview to include the upper and lower limits of fluoride from claim 19 that the injectable selenium composition contains 0.0001 µg to 2.7 µg of fluoride per 1 mL of the injectable composition, which has no art rejections under 35 U.S.C. §102/103.[1] Claim 18 has also been amended consistent with the interview to be in independent form and includes the upper and lower limits of iodine from claim 19 that the injectable selenium composition contains iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable, which also has no art rejections under 35 U.S.C. §102/103. Claims 76 and 77 have been amended to include those upper and lower limits of fluoride or iodine in claims 6, 18 and 19 and also adds the "consisting essentially of" transitional phrase. Claims 1, 4-6, 8, 9, 11, 16-19, 70 and 74-77 have been amended to remove the term "about" from these claims to overcome the 35 U.S.C. §112 rejections and advance the application.

Claim 6 has been amended to include that the composition is suitable for administration to an adult or pediatric patient when added to parenteral nutrition as recited in claim 63 and as mentioned in paragraphs [0060], [0068], [00100] and [00154] of the patent application. Claims 63 and 70 have been amended now to depend on claim 18. Claim 8 has been amended to include in addition to fluoride limits of claim 19 that the injectable selenium composition additionally contains iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable as recited in claims 18 and 19. Claim 11 has been amended to include the feature of claims 67 or 68 that the injectable composition further comprises nitric acid. Claim 66 has been amended to depend on claim 18 and includes that the selenium can be elemental selenium from selenious acid as recited in claims 13-15. Claim 67 has been amended to depend on claim 18 and includes that the selenium is in an amount of 60 µg per 1 mL of the injectable composition as recited in claims 1 and 2. Claim 68 has been amended to depend on claim 18 and includes that the selenium is in an amount of 6 µg per 1 mL of the injectable composition as recited in claims 1 and 3. Claim 79 has been amended now to depend on independent claim 18 and includes the features that the injectable composition further comprises nitric acid and has a pH of 1.8 to 2.4 as recited in claims 9, 11 and 67-68.

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[1] During the February 22, 2024 interview, the Examiner agreed that amending the independent claims to include claim 6 that has the fluoride limits or amending the independent claims to include claim 18 that has the iodine limits would overcome the art rejections of record. Claim 19 has the fluoride limits and/or the iodine limits currently claimed and was not rejected under 35 U.S.C. §102/103 based on the art of record in this Office Action.

Claim 56 has been cancelled without disclaimer. Applicant reserves the right to pursue cancelled claim 56 in one or more continuing applications.

The amendments do not add new matter. There are 29 claims pending in this application. Applicant requests that this response be considered under the After Final Consideration Pilot Program 2.0. Applicant respectfully requests entry of these amendments and allowance of the pending claims.

**1. Interview Summary**

In responding to the February 1, 2024 Office Action, Applicant's counsel, William D. Schmidt, conducted a telephone interview with Examiner Ali Soroush on February 22, 2024. Applicant thanks the Examiner for the time generously extended during the interview in which Applicant discussed proposed amendments to the claims of the current application. During the interview, the Examiner and Applicant's counsel discussed certain 35 U.S.C. §112 and 35 U.S.C. §102/103 issues and proposed amendments to the claims. Applicant discussed that removing the term "about" from the claims would remove the rejections under 35 U.S.C. §112. Applicant also discussed that amending the claims to include the upper and lower limits of fluoride in claim 6 or iodine in claim 18 that are also recited in claim 19 would overcome the rejections under 35 U.S.C. §102/103. An agreement between the Applicant and the Examiner was reached. Applicant has amended the claims consistent with the interview and, among other things, amended claim 1 to include the upper and lower limits of fluoride in claim 19 and has rewritten claim 18 in independent form to include the upper and lower limits of iodine in claim 19 consistent with the interview.

**2. Claim Rejections Under 35 U.S.C. §112**

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70 and 74-79 are rejected under 35 U.S.C. §112 as allegedly being indefinite for using the term "about" in the claims regarding the amount of selenium. Applicant respectfully disagrees and submits that the claims are clear to a person of ordinary skill in the art. Nevertheless, to advance the application without agreeing to the merits of the rejections, claims 1, 4-6, 8, 9, 11, 16-19, 70 and 74-77 have been amended to remove the term "about" from these claims to advance the application. Accordingly, the rejections under 35 U.S.C. §112 are moot.

**3. Claim Rejections Under 35 U.S.C. §102**

Claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69 and 74-79 are rejected under 35 U.S.C. §102(a)(l) as allegedly being anticipated by Selenious Acid Injection, Published 04/2019 (American Regent Label) as evidenced by Trace Element Contamination of Total Parenteral Nutrition, Contribution of Component Solutions, Published 1999 (Pluhator-Murton) and Iron contamination in parenteral nutrition mixtures, Published 11/14/2017 (Menendez). Applicant respectfully disagrees with the Office, however, to advance the application without agreeing to the merits of the rejections, Applicant has amended claim 1 consistent with the interview to include the upper and lower limits of fluoride from claim 19 that the injectable selenium composition contains 0.0001 µg to 2.7 µg of fluoride per 1 mL of the injectable composition, which has no art rejections under 35 U.S.C. §102/103. Likewise, claim 18 has also been amended consistent with the interview to be in independent form and includes the upper and lower limits of iodine from claim 19 that the injectable selenium composition contains iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable, which also has no art rejections under 35 U.S.C. §102/103. Therefore, the pending claims include the upper and lower limits of fluoride or iodine or both that are not anticipated and are not obvious in view of the cited art. Accordingly, Applicant respectfully submits that the rejections under 35 U.S.C. §102 are moot and should be withdrawn.

**4. Claim Rejections Under 35 U.S.C. §103**

The Office rejected claims 3, 11, 15, 68 and 77 under 35 U.S.C. §103 as allegedly being obvious in view of the American Regent Label as evidenced by Pluhator-Murton and Menendez. Applicant respectfully disagrees with the Office, however, to advance the application without agreeing to the merits of the rejections, as stated above, Applicant has amended claim 1 consistent with the interview to include the upper and lower limits of fluoride from claim 19 that the injectable selenium composition contains 0.0001 µg to 2.7 µg of fluoride per 1 mL of the injectable composition, which has no art rejections under 35 U.S.C. §102/103. Likewise, claim 18 has also been amended consistent with the interview to be in independent form and includes the upper and lower limits of iodine from claim 19 that the injectable selenium composition contains iodine in an amount of 0.0001 µg to 0.2 µg per 1 mL of the injectable, which also has no art

rejections under 35 U.S.C. §102/103. Therefore, the pending claims include the upper and lower limits of fluoride or iodine or both that are not obvious, and Applicant respectfully submits that the rejections under 35 U.S.C. §103 are moot and should be withdrawn.

**5. No Disclaimers or Disavowals**

Although the present communication may include alterations to the claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited reference. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history may not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

**6. Conclusion**

No fee is believed to be due with respect to filing this response. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 50-5960 for such sum.

If the Office has any questions regarding the present application, the Office is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,

/William D. Schmidt/
William D. Schmidt
Registration No.: 39,492
Attorney for Applicant

SORELL, LENNA & SCHMIDT, LLP
135 Engineer Road, Suite 110
Hauppauge, NY 11788
Tel.:(631) 656-9818
FAX: (631) 406-7146

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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# NOTICE OF ALLOWANCE AND FEE(S) DUE

109802 7590 03/22/2024

Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

| EXAMINER | |
|---|---|
| SOROUSH, ALI | |
| ART UNIT | PAPER NUMBER |
| 1617 | |

DATE MAILED: 03/22/2024

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/124,391 | 03/21/2023 | Gopal Anyarambhatla | 1848-32-CON-TRK1 | 3879 |

TITLE OF INVENTION: TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 06/24/2024 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**

# PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

109802 7590 03/22/2024
Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| |
|---|
| (Typed or printed name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/124,391 | 03/21/2023 | Gopal Anyarambhatla | 1848-32-CON-TRK1 | 3879 |

TITLE OF INVENTION: TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 06/24/2024 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| SOROUSH, ALI | 1617 | 424-630000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/124,391 | 03/21/2023 | Gopal Anyarambhatla | 1848-32-CON-TRK1 | 3879 |

109802 7590 03/22/2024

Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

| EXAMINER | |
|---|---|
| SOROUSH, ALI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

DATE MAILED: 03/22/2024

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

| Notice of Allowability | Application No. 18/124,391 | Applicant(s) Anyarambhatla et al. | |
|---|---|---|---|
| | Examiner ALI SOROUSH | Art Unit 1617 | AIA (FITF) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the filing on 03/01/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

Continuation of 3. The allowed claim(s) is/are: 1-6,8-9,11,13-19,63,65-70 and 74-79

## DETAILED ACTION

### *Notice of Pre-AIA or AIA Status*

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

### *Acknowledgement of Receipt*

Applicant's response filed on 03/01/2024 to the Office Action mailed on 02/01/2024 is acknowledged.

### *Claim Status*

Claims 1-6, 8, 9, 11, 13-19, 56, 63, 65-70, and 74-79 are pending.

Claims 7, 10, 12, 20-55, 57-62, 64 and 71-73 were previously cancelled and claim 56 is cancelled.

Claims 1, 5, 6, 8, 9, 11, 16-19, 63, 65-68, 70, 74-77, and 79 are currently amended.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 have been examined.

Claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 are allowed.

### *Priority*

Priority to CON 17/365,695 filed on 07/01/2012, which claims priority to application 63/047,708 filed on 07/02/2020.

***Withdrawn Claim Rejections - 35 USC § 112***

***Response to Applicant's Arguments***

The rejection of claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention is withdrawn in view of the amendments to the claims.

***Withdrawn Claim Rejections - 35 USC § 102***

***Response to Applicant's Arguments***

The rejection of claim(s) 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, and 74-79 under 35 U.S.C. 102(a)(1) as being anticipated by American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017) is withdrawn in view of the amendments to the claims.

***Withdrawn Claim Rejections - 35 USC § 103***

***Response to Applicant's Arguments***

The rejection of claim(s) 3, 11, 15, 68, and 77 under 35 U.S.C. 103 as being unpatentable over American Regent (Selenious Acid Injection, Published 04/2019) as evidenced by Pluhator-Murton et al. (Trace Element Contamination of Total Parenteral Nutrition. 1. Contribution of

Component Solutions, Published 1999) and Menendez et al. (Iron contamination in parenteral nutrition mixtures, Published 11/14/2017), as applied to claims 1, 2, 5, 6, 9, 13, 14, 16, 17, 18, 63, 66, 67, 69, and 74-79 above is withdrawn in view of the amendments to the claims.

***Reasons for Allowance***

The following is an examiner's statement of reasons for allowance: the prior art lacks a teaching or suggestion of a composition comprising selenium and fluoride in an amount of 0.0001-2.7µg. The prior art teaches composition comprising selenium. The prior art also teaches composition comprising fluoride. However, the prior art does not teach or suggest a composition having fluoride in an amount of 0.0001-2.7µg. Therefore, claims 1-6, 8, 9, 11, 13-19, 63, 65-70, and 74-79 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is

encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617